

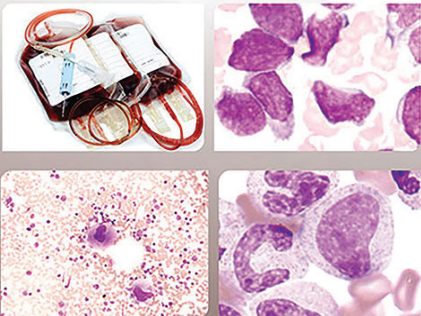


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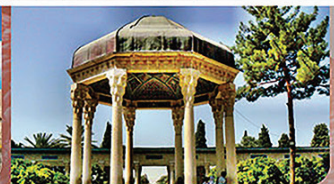
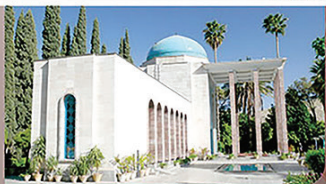
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- Hemoglobinopathies
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- Hematopoietic Stem Cell Transplantation
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Novel Iron-Chelation Therapies in Thalassemia

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Abstract

Iron overload is one of the main culprits of disease-related morbidity in thalassemia. While transfusion therapy is the primary mechanism of iron overload in transfusion-dependent thalassemia (TDT), hepcidin dysregulation is at the core of increased iron parameters in patients with non-transfusion-dependent thalassemia (NTDT). Iron-chelating drugs include deferoxamine, which is given parenterally, and deferasiprone and deferasirox, which are given orally. Whereas these 3 agents are currently available in TDT, deferasirox remains to be the only chelator to have received the Food and Drug Administration and European Medicines Agency approval in NTDT based on results from the THALASSA trial.

However, adherence to long-term chelation therapy is crucial in preventing iron overload-related complications. For example, barriers to optimal adherence to deferasirox dispersible tablets (DT) include palatability, preparation time, and requirements for a fasting state at the time of dosing. A new film-coated tablet (FCT) formulation was developed, which is swallowed once-daily, whole or crushed, with or without a light meal. This open-label, phase II ECLIPSE study also evaluated patient-reported outcomes in TDT or lower-risk myelodysplastic syndrome patients randomized to receive deferasirox DT or FCT over a 24-week period. FCT recipients consistently reported better adherence, greater satisfaction, and fewer concerns, with a safety profile consistent with the known DT formulation. These findings suggest a preference in favor of the new formulation, with better patient satisfaction and adherence translating into reduced iron overload-related complications. The utility of this new formulation in patients with NTDT, alongside other novel iron chelators, remains to be investigated.

Keywords • Deferasirox • Deferasirox dispersible tablet • Deferasirox film-coated tablet • Iron chelation therapy • Thalassemia • Patient-reported outcome (PRO)

Transfusion versus Splenectomy in Thalassemia: Pros and Cons

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Abstract

Thalassemia is a genetic disorder of the hemoglobin classified according to transfusion dependence into transfusion-dependent thalassemia (TDT) and non-transfusion-dependent thalassemia (NTDT). In thalassemia, there is an overabundance of defective red blood cells, which leads to splenomegaly related to an enlarged hyperfunctioning spleen. Splenectomy, however, should be restricted to certain indications in view of the associated increased risk of venous thrombosis, pulmonary hypertension, and overwhelming post-splenectomy infections. The main indications for splenectomy in both TDT and NTDT are: 1) hypersplenism leading to cytopenia and 2) splenomegaly heralding imminent rupture or accompanied by left upper quadrant pain or early satiety. Splenectomy is also indicated in TDT patients with increased blood requirement, preventing adequate control with iron chelation therapy, and in NTDT patients with worsening anemia leading to poor growth and development.

On the other hand, while TDT patients must receive regular blood transfusions for survival, occasional transfusions should be considered in NTDT patients in settings with anticipated acute stress or blood loss such as pregnancy, surgery, or infections, and in the prevention or management of certain complications such as leg ulcers, thrombotic events, silent brain infarcts, pulmonary hypertension, and extramedullary hematopoietic pseudotumors. The potential complications of blood transfusions are iron overload, risk of alloimmunization, and transfusion-transmitted infections.

It is, therefore, evident that both splenectomy and blood transfusions are associated with risks and benefits. Transfusion therapy is a survival requirement in TDT, but transfusions in NTDT and splenectomy in thalassemia should have their pros weighed against their potential hazards in every treated patient.

Keywords • Non-transfusion-dependent thalassemia • Splenectomy • Transfusion-dependent thalassemia • Transfusion

New Challenges in Acute Lymphoblastic Leukemia

Robin Foà

Abstract

Acute lymphoblastic leukemia (ALL) can affect individuals of all ages. In childhood, it is the most frequent cancer. A modern approach requires a rapid, broad and integrated biological work-up at presentation. This enables an accurate diagnosis, stratification of patients into prognostic subgroups, treatment algorithms, targeted therapies (when applicable), and monitoring of minimal residual disease (MRD). Most protocols today personalize treatment, including transplantation, according to the MRD status.

The outcome of childhood ALL has progressively improved with cure rates of $\approx 80\%$. In adults, prognosis is still unsatisfactory, despite improvements in young adults with pediatric-like regimens. Important advancements have instead occurred in Ph+ ALL, the most frequent and unfavorable adult subgroup. Tyrosine kinase inhibitors (TKI), both alone and in combination with chemotherapy, have changed the management and outcome of Ph+ ALL. It is, thus, mandatory that the abnormality be rapidly investigated at presentation. Even elderly patients respond to TKI and steroids alone given upfront, with no systemic chemotherapy, with complete remissions close to 100%.

Monoclonal antibodies (MoAb) are being actively used. Very encouraging results have been obtained with the bispecific (anti-CD19 and CD3) MoAb blinatumomab in relapsed/refractory (R/R) ALL and in MRD+ patients. Activity has also been reported in R/R ALL patients with the anti-CD22 MoAb conjugated to calecheamicin, inotuzumab ozogamicin. Finally, the impact of rituximab in the 1st-line management of CD20+ ALL has been recently documented.

Advancements in technologies are also opening new avenues toward the identification of further subgroups of ALL which in the future may benefit from innovative/targeted therapeutic strategies.

Keywords • Acute lymphoblastic leukemia • Prognostic stratification • Algorithms of treatment • Targeted therapy • Minimal residual disease

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Changing Landscape in the Management of Chronic Lymphocytic Leukemia

Robin Foà

Abstract

Chronic lymphocytic leukemia (CLL) is the most frequent leukemia in the Western hemisphere accounting for 25% to 30% of all leukemias, while it is rare in other geographic areas (e.g., Japan). The median age at presentation is around 70 years. In view of the progressive extension of the median life expectancy, the prevalence of CLL is increasing. CLL is also diagnosed in a notable proportion of younger individuals because of a greater use of routine blood tests. For decades it has been known that CLL is a disease with a highly heterogeneous clinical course and overall prognosis. The possibility of identifying biological features with prognostic implications has progressively modified our overall approach to patients with CLL.

A precise diagnostic workup and a better prognostic stratification of CLL nowadays acquire further importance because of the many therapeutic options available. We no longer rely only on chlorambucil (Chl), but also on purine analogs, monoclonal antibodies, combined use of chemotherapy and monoclonal antibodies, and stem cell transplantation. Many chemoimmunotherapy combinations are used such as FCR (fludarabine, cyclophosphamide, and rituximab), BR (bendamustine, R), and Chl-R/ofatumumab/ obinutuzumab.

Drugs capable of targeting pathways downstream of the B-cell receptor have ingenerated great expectations. A downstream target of the B-cell receptor is represented by the Bruton tyrosine kinase (BTK), and a new class of drugs (the 1st being ibrutinib) capable of inhibiting BTK have shown very promising results. A PI3 kinase delta inhibitor, idelalisib, is also very active in CLL, as well as the Bcl-2 inhibitor venetoclax. Although a specific genetic abnormality is not linked to CLL, we have entered an era of the biologically-driven management of CLL.

Keywords • Chronic lymphocytic leukemia • Algorithms of treatment • Chemoimmunotherapy • Mechanism-based treatment • Minimal residual disease

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Role of the Laboratory Today in an Optimal Workup of Chronic Lymphocytic Leukemia

Anna Guarini

Abstract

A broad biologic characterization is today possible in chronic lymphocytic leukemia (CLL) through an integrated approach based on an accurate morphologic, immunophenotypic, cytogenetic, and molecular characterization. The aims are to enable a precise differential diagnosis between CLL and other B-cell chronic lymphoproliferative disorders, including non-Hodgkin's lymphomas in leukemic phase. On well-prepared and stained slides, the morphology of CLL is usually typical, with the characteristic presence of smudge cells. Atypical morphologic features may suggest the presence of a different condition, which needs to be defined with other laboratory investigations. CLL presents a characteristic immunophenotypic profile: CD19+, CD5+, CD20±, SIg±, CD23+, CD22-(+), and CD200+. Typically, CLL cells are CD5+ and show low levels of surface Ig and of CD20.

Once a correct diagnosis of CLL is made, different biologically-based prognostic markers can be investigated: CD38, CD49a, FISH, IGHV status, TP53, etc. A number of issues need to be taken into account: 1) Should all these prognostic markers be investigated? 2) Do they impact on our treatment decisions? 3) If yes, which tests should be performed and when? 4) On all patients, irrespective of age?

At present, the only biologic parameters that can effectively guide treatment are the presence of a 17p deletion and/or TP53 mutation. These markers should be investigated at the time of 1st treatment and in relapsed/refractory cases. The prognosis of patients carrying an 11q deletion, initially associated with a poor outcome, has changed following the use of FCR and, more in general, of rituximab-based strategies.

In the era of mechanism-based drugs, a biologically-based prognostic stratification has today important therapeutic implications.

Keywords • Chronic lymphocytic leukemia • Diagnostic workup • Prognostic stratification • FISH • TP53

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New Challenges in Hematopoietic Stem Cell Homing and Engraftment

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Abstract

While the alpha-chemokine stromal-derived factor-1 (SDF-1)—CXCR4 and very late antigen-4 (VLA-4)—vascular adhesion molecule-1 (VCAM-1) axes play an unquestionably important role in the retention of hematopoietic stem/progenitor cells (HSPCs) in the bone marrow, new evidence shows that, in addition to SDF-1, the migration of HSPCs is directed by the gradients of bioactive lipids such as sphingosine-1 phosphate (S1P) and ceramide 1-phosphate (C1P) and certain extracellular nucleotides, including adenosine triphosphate (ATP). Furthermore, the SDF-1 chemotactic gradient may be positively primed/enhanced by some cationic peptides such as C3a, LL-37, and beta 2-defensin and HSPCs respond robustly, even to very low SDF-1 gradients in the presence of these priming factors. Overall the retention of HSPCs in bone marrow niches involving the SDF-1—CXCR4 axis is an active process that counteracts high S1P gradient present in peripheral blood and thus prevents the egress of HSPCs. Moreover, since S1P, C1P, ATP, C3a, LL-37, and beta 2-defensin are upregulated in the bone marrow after myeloablative conditioning for transplantation, a more complex picture of HSPCs homing emerges. Moreover, the mobilization/egress of HSPCs from the bone marrow into peripheral blood is orchestrated by 3 ancient interacting-with-each-other proteolytic cascades activated in the mannan-binding lectin pathway including complement-, coagulation-, and fibrinolytic-cascade. While the activation of the complement cascade triggers and executes the egress of HSPCs from the bone marrow into peripheral blood, both heme oxygenase-1 and inducible nitric oxide, which have a well-documented anti-inflammatory potential, play opposite roles. These observations may lead to the development of more efficient mobilization and homing/engraftment promoting strategies for HSPCs.

Keywords • Hematopoietic stem cells • Mobilization • Homing
• SDF-1 • CXCR4

VSELs Therapy in Hematological Disorders

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Abstract

Regenerative medicine is searching for stem cells with the potential to differentiate into all germ layers. Evidence having accumulated shows that adult tissues harbor a population of dormant rare stem cells endowed with broad differentiation potential, termed “very small embryonic-like stem cells” (VSELs), which display several epiblast/germline markers, suggesting their embryonic origin and developmental deposition in adult tissues. Recently, we found that VSELs do express several sex hormone (SexHs) receptors and respond *in vivo* to SexHs stimulation. Moreover, since VSELs share several markers characteristic of migrating primordial germ cells (PGCs) and can be specified into long-term hematopoietic stem cells (LT-HSCs) and mesenchymal stem cells (MSCs), this observation sheds new light on the bone marrow stem cell hierarchy. Nevertheless, in spite of the expression of pluripotent stem cell markers, changes in the epigenetic signature of imprinted genes (e.g., by erasure of imprinting at the Igf-2–H19 locus) in VSELs are involved in their resistance to Igf-1/Igf-2 signaling and keep these cells in adult tissues in quiescent state. As reported in several emergency situations related to organ damage (e.g., heart infarct, stroke, and skin burns), VSELs can be mobilized into peripheral blood and contribute to tissue organ/regeneration. Recently, to bring these cells for potential clinical applications, we developed an efficient *ex vivo* expansion strategy for these cells in a chemically defined medium supplemented with FSH, LH, and BMP-4 after the activation of DNMT3L in these cells to re-methylate erased imprinted loci, which allows them for effective *ex vivo* expansion (e.g., for potential hematological applications).

Keywords • Hematopoiesis • Hematopoietic stem cells • VSELs • Stem cell expansion

Novel Therapies in Acute Myeloid Leukemia

Farhad Ravandi-Kashani

Abstract

The discovery of recurrent molecular abnormalities in acute myeloid leukemia (AML) has led to the development of novel agents targeting these mutations. FLT3 mutations occur in approximately 30% of patients with AML and a number of FLT3 inhibitors are in clinical trials, including sorafenib, midostaurin, quizartinib, crenolanib, and gilteritinib. The randomized RATIFY trial has demonstrated that a combination of standard-induction chemotherapy with midostaurin in younger patients with FLT3-mutated AML leads to superior survival than chemotherapy alone.

Isocitrate dehydrogenase (IDH) is an enzyme of the Krebs cycle; mutations in either IDH1 or IDH2 occur in 20% of patients with AML. These mutations lead to a hypermethylated DNA signature and a block of normal cellular differentiation. Both IDH1 (AG-120) and IDH2 (AG-221) inhibitors have shown promising activity in AML. More recently, the BCL-2 inhibitor, venetoclax, showed high response rates observed in untreated elderly patients when venetoclax was given in combination with hypomethylating agents or low-dose cytarabine.

Despite comprehensive molecular profiling, many patients are not found to have actionable mutations; alternative treatment strategies such as antibody-based therapies are, therefore, needed in this population. Novel antibody-drug conjugates such as SGN-CD33 have been developed and are in clinical trials.

In summary, the tremendous recent progress in understanding the biology of leukemogenesis and development of novel, non-cytotoxic agents gives optimism that such therapies have the potential to result in durable remissions and possibly even cures for some patients in AML.

Keywords • AML • Molecular targets • Targeted therapies • Monoclonal antibodies

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Blood Group Genotyping

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Abstract

Blood group antigens, present on the cell membrane of blood cells, are classically identified by serology using patient sera or monoclonal antibodies. At present, the molecular basis of the 36 blood group systems and 17 human platelet antigens is known. This makes it possible to predict the phenotype based on the genotypes of genes encoding for these antigens. Most reference laboratories use in-house and/or commercially available blood group genotyping tests for this purpose. In the past, these assays were mainly used for patients whose red cells could not be used for serological typing due to the presence of auto-antibodies, after recent transfusions or for fetal genotyping, and to solve unexplained serological findings. However, in later years, DNA genotyping is increasingly used to replace serology. For example, if multiple alloantibodies or alloantibodies against a high-frequency antigen are present, it is more efficient to directly genotype the patient and then to start with extensive serological investigations. Also, blood banks are starting to implement genotyping of donor cohorts for multiple blood group antigens, including high-frequency antigens, to be able to provide matched donor blood for alloimmunized patients or for patient groups at high risk for alloimmunization (e.g., hemoglobinopathy patients). Serological typing of large cohorts of donors is labour-intensive and expensive; moreover, it is hampered by the lack of sufficient amounts of typing reagents for all blood group systems of interest. High-throughput genotyping methods provide a feasible approach to obtain a large pool of comprehensively-typed blood donors.

Keywords • Blood group antigens • Blood grouping and crossmatching • Genotyping techniques

Post-Splenectomy Recurrent Thrombosis in Thalassemia Intermedia Patients as a Huge Dilemma: Case Presentation and Treatment Options

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Abstract

Introduction: Post-splenectomy thrombophilia is one of the major concerns regarding thalassemia intermedia (TI) patients. We introduce a TI patient, who developed multiple extensive thrombotic events after splenectomy.

Case Presentation: A 30-year-old female patient underwent splenectomy. After presenting with the 1st episode of portal vein thrombosis, she was put on warfarin to achieve an INR level of around 2 to 3. She, however, developed recurrent episodes of thrombosis and had another hospital admission despite the antithrombotic therapy. She was placed on a regular transfusion program, with minor effects. In thrombophilia assessment, she was only heterozygously positive for MTHFR (G677T) and MTHFR (A1298C), and homozygously positive for PAI-1 (4G).

Discussion: As post-splenectomy thrombophilia can develop in any TI patient, a short-course antithrombotic therapy is considered pre and post operation for all TI patients. We have met only a few post-splenectomy cases suffering from huge thrombophilia with a history of multiple recurrent extensive thromboses that could not be controlled with an appropriate dose of anticoagulants and a regular transfusion program. Literature review shows different cases with the problem; however, all of them have been controlled by anticoagulant therapy.

Conclusion: Although short-course antithrombotic treatment may be enough for the majority of TI patients following splenectomy, our patient clearly shows the thrombophilia effects of splenectomy in an individual genetically exposed to thrombophilia. We, therefore, recommend thrombophilia panel tests for all TI patients candidated for splenectomy.

Keywords • Thalassemia intermedia • Splenectomy • Thrombophilia

Antifungal Resistance in Cancer Patients

Parisa Badiee

Abstract

Pathogenic fungi (especially *Candida* and *Aspergillus*) are associated with high morbidity and mortality rates in cancer patients. Antifungal resistant phenomons are emerging in some genera. *Candida spp* are the most common cause of candidemia in many countries, and some types of *Candida* are becoming resistant to 1st-line (fluconazole) and 2nd-line antifungal agents (echinocandins; anidulafungin, caspofungin, and micafungin). Approximately 7% of all *Candida* isolated from patients, especially *Candida glabrata*, and up to 8% of *Candida glabrata* isolates in 2014 were resistant to fluconazole and echinocandins, respectively. Multi-drug resistant *Candida* infections (resistant to both fluconazole and an echinocandin), are reported. Prevalence of azole resistance in the *Aspergillus* family is reported approximately to range between 3% and 6%. Previous exposure to certain antifungal medications and use of agricultural azoles may lead to resistant species.

One of the most important factors in decreasing drug resistance is the appropriate use of antifungal agents. According to the CDC's suggestions, developing new laboratory tests for tracking trends in antifungal resistance by species confirmation and antifungal susceptibility testing, using genetic sequencing to identify the specific mutations associated with antifungal resistance, hospital and environmental infection control guidelines, and staff groups can help with the management of these diseases in immunocompromised patients.

Keywords • *Candida glabrata* • Fluconazole • Echinocandins

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Urgent Need for Antifungal Stewardship Program in Hematology/Oncology Wards

Ali Amanati

Abstract

Infection-related mortality in children with malignancy is comparable to treatment-related mortality, which necessitates implementation of the antifungal stewardship program (ASP) to achieve timely diagnosis, to increase targeted antibiotic therapy, to reduce the use of broad-spectrum antibiotic, to improve patient outcome, to decrease hospital stay, and finally to lessen costs. Multi-drug resistance (MDR) has emerged in recent decades. Limited new resources of antibiotics for these MDR organisms along with limited reliable diagnostic modalities change our current approach to diagnosis and treatment widely.

Changes in the local epidemiology of bacterial and fungal infections in neutropenic patients, changes in the susceptibility of restricted antibiotic and antifungal agents, surveillance of most prescribed antibiotic and antifungal agents, and burden of *Clostridium difficile*-associated colitis need to be determined constantly in each oncology center.

Prevention of catheter-related blood stream infections by “preventive bundle” measures should be implemented, especially in high-risk patients.

Educational materials for stewardship, preauthorization and/or prospective audit and feedback, and facility-specific clinical practice guidelines are core components of any stewardship program.

These components should be organized under an ASP program director, an infectious disease clinician, and the requisite interpersonal, diplomatic, and organizational skills to assure ASP implementation and coordination to achieve its goals.

Keywords • Hematology/oncology • Antimicrobial stewardship
• Infectious diseases

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Mixed-Phenotype Acute Leukemia: Challenges in Diagnosis and Treatment

Mohammadreza Bordbar

Abstract

Background: Mixed-phenotype acute leukemia (MPAL) is a very rare entity in which leukemic blasts present both myeloid and lymphoid markers. Alongside difficulties in diagnosis and classification, the best treatment strategy is another challenging topic.

Results: MPAL, which was previously defined as biphenotypic acute leukemia (BAL), is an undifferentiated leukemia or an acute leukemia of ambiguous lineage and represents between 3% and 5% of acute leukemias. The European Group for Immunological Classification and Characterization of Acute Leukemias (EGIL) in 1995 published a point scoring system to define BAL. In the EGIL classification, BAL was diagnosed if a score greater than 2 was given to both myeloid and lymphoid lineages. Lack of the specificity of certain EGIL-proposed markers, using varying and arbitrary thresholds of cellular antigen expression to qualify as positive, and failing to incorporate cytogenetic data were the major shortcomings of this classification. In 2008, the World Health Organization (WHO) proposed new criteria for defining lineage assignment in acute leukemia. In this new classification, the term BAL was no more used, and MPAL was introduced. Moreover, the criteria for lineage assignment were simplified, and no scoring system was used any more. In addition, some cytogenetic alterations were incorporated into the classification.

There is still much uncertainty concerning the best treatment approach for MPAL. Most retrospective clinical trials have demonstrated that ALL-like induction regimens lead to high remission rates and low toxicity compared to AML-like induction or a combination of ALL and AML protocols.

Another challenging issue is the post-remission treatments, including allogenic hematopoietic stem cell transplantation (HSCT). Some experts recommend alloHSCT in the 1st remission if suitable donors are available. They claim that this may lead to more durable remissions than chemotherapy-alone regimens. However, some other investigators believe that alloSCT should be offered to patients with adverse cytogenetic and clinical features such as infantile leukemia and poor response to therapy.

Conclusion: MPAL is a rare subtype of leukemia with a poor prognosis. The optimal treatment approach is still unclear. Most experts recommend ALL-like induction regimens. The need for alloSCT is a matter of debate, although most investigators believe that it should be done with adverse clinical and cytogenetic risk factors.

Keywords • Mixed-phenotype acute leukemia, Undifferentiated leukemia, Diagnosis, Therapy

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New Insight into the Laboratory Diagnosis of Non-Immune Hereditary Red Cell Membrane Disorders

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Abstract

Hereditary red blood cell (RBC) membrane defects can lead to some non-immune hemolytic disorders like hereditary spherocytosis, hereditary elliptocytosis, hereditary ovalocytosis, and hereditary stomatocytosis. A lipid bilayer structure of the membrane and different skeletal proteins are responsible for deformability and mechanical stability in RBCs. Different mutations in genes encoding the RBC membrane protein are the cause of the above-mentioned disorders. Some affected individuals are clinically asymptomatic or have mild hemolysis, while others need early diagnosis in order to manage their anemia and also hyperbilirubinemia. There are different laboratory approaches that can be used for the diagnosis of different kinds of RBC membrane disorders. Assessment of peripheral blood smear for finding abnormal morphologies is very helpful as the 1st-line of evaluation. Other tests like osmotic fragility, acidified glycerol lysis time test, and flowcytometry-based EMA-binding assay can be used as screening tests for hereditary spherocytosis. Ektacytometry, membrane protein analysis by SDS, polyacrylamide gel electrophoresis, and next generation sequencing for revealing the exact membrane protein gene mutations behind hemolysis are other techniques that can be used for membrane defect diagnosis.

Keywords • Red cell membrane • Hereditary spherocytosis • Hereditary elliptocytosis • Hereditary stomatocytosis

Immune Cell Therapy in Hematologic Malignancies

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Abstract

A significant proportion of hematological malignancies remain limited in treatment options. Immune system modulation serves as a promising therapeutic approach to eliminating malignant cells. Immune cell therapy (ICT) for hematologic malignancies is a multidisciplinary basic, translational, and clinical research effort whose overall goal is to improve outcomes for patients with hematologic malignancies. The broad, long-term goal of ICT is to build on and extend the current knowledge in the fields of leukemia, lymphoma, myeloma, and hematopoietic cell transplantation and to develop and implement novel strategies for improving therapeutic results in these patients. These can be divided into: 1) tumor microenvironment, 2) bone marrow niche, 3) hematopoietic stem cells, 4) NK cells, 5) dendritic cells, and 6) selected $\gamma/\Delta T$ cells and CAR-T cell therapies. There are many clinical trials with over 500 active clinical trials and more than 200 trials specific for hematologic malignancies and transplantation. These range from phase I “first in humans” to randomized phase III studies. The application of optimal measures, incorporating genome editing and gene transfer technologies, can enhance efficacy, reduce toxicity, and facilitate future development and clinical incorporation of this rapidly advancing technology.

Keywords • CAR-T cells • NK cell • DC • Cancer

Comparison of Quality of Life in Patients with Beta-Thalassemia Intermedia and Beta-Thalassemia Major in Southern Iran

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Abstract

Background: Increased life expectancy in patients with beta-thalassemia requires health professional care to improve their quality of life. We sought to evaluate health-related quality of life (HRQoL) and its determinants in patients with beta-thalassemia intermedia (B-TI) compared with patients with beta-thalassemia major (B-TM).

Methods: In this cross-sectional study, 118 patients with B-TI referring to the Thalassemia Clinic of Shiraz University of Medical Sciences were investigated by convenience sampling from January to June 2014 in southern Iran. Short Form-36 questionnaire was used. Previously we conducted a similar study on 101 patients with B-TM (12 to 38 years old). The data of the 2 studies were compared and analyzed.

Results: Mean age was 26.5 ± 6.5 (12–48) years in the B-TI group and 19.5 ± 4.4 (12–38) years in the B-TM group. The best scales of HRQoL were PF (76.8 ± 26.6) and BP (70.1 ± 24.8) in the B-TI patients. Moreover, the males were significantly better in VT, SF, and MH than the females ($P < 0.05$). Education showed a significant association with the total HRQoL score in B-TI ($B = -6.3$, $P = 0.048$). After adjusting for the covariates, total HRQoL was similar between the 2 groups. In evaluating the subscales, only PF showed a better condition in the patients with B-TM (adjusted mean difference = 12.5, 95% CI: 5.6 to 19.3; $P < 0.0001$).

Conclusion: Contrary to our expectations, HRQoL in the patients with B-TI was not better than that in those with B-TM. Training programs and psychosocial support of the patients and their caregivers with focus on female patients and patients with lower educational and socioeconomic levels should be provided.

Keywords • Beta-thalassemia • Health • Quality of life • SF36

Increased Level of Fetal Hemoglobin by an LSD1 Inhibitor, GSK-LSD1, in Adult Erythroid Cells

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Abstract

Background: The switch from fetal γ to β globin gene expression occurs at birth. The genetic regulation of this switch has been studied for decades, and the change in molecular mechanisms in the gene expression has been elucidated. Increased levels of fetal hemoglobin are associated with decreased symptoms and increased life span in patients with sickle-cell disease (SCD) and β -thalassemia. Hydroxyurea is a drug for SCD. It is not, however, beneficial in the cure of the patients, necessitating new drugs or agents. Recently it was shown that lysine-specific demethylase-1 (LSD1), an enzyme that removes monomethyl and dimethyl residues from the lysine 4 residue of histone H3, is a repressor of γ -globin gene expression. In this report, we investigated the inhibition of LSD1 by the GSK-LSD1 inhibitor in human erythroid CD34 cells to increase γ globin.

Methods: We examined the effects of the GSK-LSD1 inhibitor on CD34 cells *ex vivo*. We treated the cells with 0, 0.5, 1.5, and 5 μ M of the GSK-LSD1 inhibitor on days 4 to 14 of the differentiation culture. Then we performed an analysis of the expression of LSD1 and γ globin genes with real-time PCR using the IQ SYBR Green Master mix.

Results: After treatment in a 1.5- μ M concentration of the inhibitor, the mean of γ -globin mRNA expression was induced up to 33-fold. We observed a decrease in the LSD1 mRNA expression.

Conclusion: Our results indicated that LSD1 played an important role in γ -globin silencing in adult erythroid cells. Further, the GSK-LSD1 inhibitor might be used to treat SCD and β -globinopathies, with an increase in concentration for HbF induction within the therapeutic plasma concentration.

Keywords • γ -globin • Lysine-specific demethylase-1 • Sickle-cell disease

Presentation of a Computing System and Algorithm for Differentiating Beta-Thalassemia Traits from Iron Deficiency Anemia

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Abstract

The prevalence of beta-thalassemia traits (BTTs) is estimated to be 240,000,000 cases around the world, and these patients are centralized on the thalassemia world belt map. Marriage of couples with BTTs can result in beta-thalassemia major in their next generation. Every country located in the thalassemia world belt map has applied a kind of screening test to find the symptomless cases of BTTs and to impose some preventive conditions for the marriage of couples who both have BTTs. The most efficient screening tools are those that can differentiate between the 2 most common microcytic anemia conditions: BTTs and iron deficiency anemia. For example, the NESTROFT (Naked Eye Single Tube Red Cell Osmotic Fragility Test) has been used as a screening tool in India. Unfortunately, none of the current screening tests has sufficient sensitivity or specificity. We compared the red blood cell (RBC) indices of 250 patients with BTTs and 250 cases with iron deficiency in the city of Esfahan in Iran from 2011 to 2016. We used a novel algorithm in the form of software whose inputs were RBC indices and found significant differences between the BTT results and the results of iron deficiency anemia. To find out the specificity and the sensitivity of our new screening tool, we put the data of 100 patients with BTTs and 100 patients with iron deficiency in the algorithm and estimated a sensitivity of 93% and a specificity of 94% for the diagnosis of BTTs from iron deficiency.

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Keywords • Beta thalassemia trait • Iron deficiency anemia • Screening • Software

Correlation between Pancreatic Iron Overload Measured by T2*-Weighted MR Imaging and Diabetes Mellitus in Patients with β -Thalassemia Major

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Abstract

Diabetes mellitus (DM) is one of the potential complications in patients with transfusion-dependent β -thalassemia major (β -TM). Chronic iron overload is the main laboratory indication of DM occurring as a result of this condition. In this case-controlled study performed in 2016, we examined pancreatic iron levels in outpatients with β -TM at the Thalassemia Research Center in the north of Iran. In this study (the design of which was approved by the center's ethics committee), cases of patients with β -TM and DM were gender- and age-matched with control subjects, who were nondiabetic and had normal blood glucose on standard oral glucose tolerance tests. One of 4 diagnoses (normal, prediabetes, impaired glucose tolerance, and DM) was made according to the American Diabetes Association (ADA) criteria. T2*-weighted magnetic resonance (MR) imaging of the heart, liver, and pancreas was performed using a 1.5 Tesla scanner (Achieva, Philips Medical Systems). The Pearson coefficient test for the correlation of quantitative variables was used, and the Student *t*-test was applied to compare the quantitative variables. The χ^2 test was used to find a statistically significant cutoff and odds ratio (OR) for normal or abnormal glucose metabolism shown on the T2*-weighted MR imaging of the pancreas. A receiver operating characteristic (ROC) curve was developed for the iron levels in the pancreas on the T2-weighted MR imaging. A P value less than 0.05 was considered a statistically significant difference. The study enrolled 26 diabetic cases, 17 nondiabetic cases, and 8 cases of impaired glucose tolerance or prediabetes. There were no statistically significant differences in the basic and clinical characteristics between the 3 groups. The severity of pancreatic and cardiac iron siderosis was significantly different between the groups. We found a statistically significant difference at 5.6 ms in the T2*-weighted MR imaging values for the pancreas between the patients with normal versus abnormal glucose metabolism [$P < 0.009$, OR: 11.2 (95% CI: 1.32 to 94.4)]. The ROC curve for the 5.6 ms cutoff led to an area under the curve (AUC) of 0.69 (95% CI: 55 to 84; $P < 0.02$), with sensitivity and specificity of 94% and 42%, respectively. There was a moderate positive correlation between the pancreatic and cardiac T2*-weighted MR imaging ($r = 0.4$; $P < 0.001$) and a weak correlation between the pancreas and the liver ($r = 0.38$; $P < 0.005$). To conclude, we introduce a cutoff of 5.6 ms on T2*-weighted MR images of the pancreas for the prediction of abnormal glucose metabolism in β -TM patients.

Keywords • Thalassemia major • Magnetic resonance imaging • Pancreas • Diabetes mellitus • Iron overload

Comparison of Central Nervous System Relapse in Children with Acute Lymphoblastic Leukemia; Treated with Intrathecal Methotrexate alone and Triple Intrathecal Therapy

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Abstract

Background: Adding cytarabine and hydrocortisone to intrathecal methotrexate (IT MTX) prophylaxis had positive effects in reducing central nervous system (CNS) relapses and survival in childhood acute lymphoblastic leukemia (ALL). The present study aimed to compare the incidence of CNS relapses and survival between two modalities of CNS prophylaxis (IT MTX and triple IT therapy) in ALL patients.

Methods: Two hundred children, aged 1-10 years with the diagnosis of ALL and treated with IT MTX or triple IT as CNS prophylaxis, were studied. Data on gender, age at diagnosis, blood cell count, cerebrospinal fluid (CSF) analysis, treatment protocol, and modality of CNS prophylaxis was collected from patients' medical records. CNS relapses during treatment, the first year after discontinuation of treatment, and 3-year disease-free survival (3-DFS) was determined.

Results: The mean age of patients at diagnosis was 5.65 ± 3.14 years and 47.2% were boys. A total of 108 patients were treated with IT MTX and 92 patients with triple IT. The incidence of CNS relapse in the IT MTX group was 24.1% and in triple IT therapy 9.8% ($P=0.004$). More CNS relapses in both groups were early. Three years disease-free survival was higher in the triple IT therapy than IT MTX group (82.6% and 71.4%, respectively) ($P=0.01$).

Conclusion: Although IT MTX is a favorable treatment for the prevention of CNS relapse in childhood ALL, but it is more effective when accompanied with cytarabine and hydrocortisone than IT MTX alone.

Keywords • Leukemia • Therapeutics • Recurrence

Hematopoietic Stem Cell Transplantation for Childhood Leukemia in MAHAK

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Abstract

Background: The cure rate of childhood acute lymphoblastic leukemia (ALL) has improved considerably and approaches 80% today. However, the outcomes of patients who suffer from leukemic relapse remain unsatisfactory. Despite the high cure rate of children and adolescents with ALL, a subgroup of patients benefit from allogeneic hematopoietic stem cell transplantation (HSCT). Allogeneic HSCT remains the standard treatment for intermediate-/high-risk AML patients.

Methods: We recruited 62 patients, 45 with ALL and 17 with acute myeloid leukemia (AML). The patients' age ranged between 1 and 20 years, with a median age of 11 years. There were 34 males and 28 females (M/F ALL=26/19, AML=8/9). The patients underwent stem cell transplantation in our hospital from 2012 to 2016. Sixty-one patients received allogeneic HSCT and 1 patient with AML received autologous HSCT. Fifty-two patients transplanted 6/6 matched and 9 patients 5/6 matched.

Results: In allogeneic peripheral blood stem cell transplantation (PBSCT) ALL patients, the median time to an absolute neutrophil count greater than $0.5 \times 10^9/L$ was 12 days and the median time to a platelet count greater than 20×10^9 was 15 days, as opposed to 17 and 21 days in the allogeneic bone marrow ALL patients. In the allogeneic PBSCT ALL patients, the hospitalization period was 36 days, as opposed to 45 in the allogeneic bone marrow ALL patients. At a median follow-up of 32.5 months (4–48 mon) after transplantation, the event-free survival rate was 68% and 3-years' overall survival rate was 63% in the AML patients.

Conclusion: HSCT can lead to durable remissions in children and adolescents with leukemia and increase in the survival of children. PBSCT in childhood ALL was consistent with significantly faster absolute neutrophil count and platelet recovery in allogeneic PBSCT and hospitalization was shorter. Longer follow-up is required to fully evaluate the efficacy and long-term results.

Keywords • Busulfan • Leukemia • MAHAK

Effects of Hypoxia on some Biological Behaviors of Human Leukemia T-Cell Line Co-Cultured with Bone Marrow Mesenchymal Stem Cells

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Abstract

Background: One of the most important problems in the treatment of leukemia is the expansion of resistance to chemotherapeutic agents. Therefore, assessing the drug resistance and especially drug resistance genes of leukemic cells are important in any treatment. The impact of mesenchymal stem cells (MSCs) and hypoxic condition have been shown in many of the biological performance of leukemic cells.

Methods: MOLT-4 cells were co-cultured with MSCs in the hypoxic condition induced by Cobalt chloride (CoCl₂) for 6 and 24 hours. Then, apoptosis of cells was analyzed using annexin V/PI staining and expression of the drug resistance genes, including MDR1, MRP, and BCRP along with apoptotic and anti-apoptotic genes, including BAX and BCL2, were evaluated by real-time PCR.

Results: A hypoxic condition for MOLT-4 cells co-cultured with MSCs could increase the expression of MDR1 and BCRP genes ($P < 0.05$) which are involved in drug resistance. In addition, our results showed that this condition increases the expression of BCL2 ($P < 0.05$) and reduce the apoptosis in MOLT-4 cells co-cultured with MSCs in hypoxic condition.

Conclusion: Our observations suggest that CoCl₂ induced hypoxia could have an inhibitory effect on ALL lineage MOLT-4 cells co-cultured with MSCs that is hypoxia independent, and in some cases, hypoxia and MSCs can contribute to increased drug resistance genes and less apoptosis in ALL cells as well. These effects can represent the role of hypoxia and MSCs on the biological behavior of ALL cells that may lead to particular treatment outcomes.

Keywords • Acute lymphoblastic leukemia • Mesenchymal stem cell • Drug resistance • Hypoxia • Co-culture • Apoptosis

Protective Role of Ursodeoxycholic Acid and Vitamin E in the Prevention of MTX-Induced Liver Injury in Pediatric Patients with Leukemia: A Randomized Clinical Trial

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Abstract

Background: Methotrexate is accused to cause liver fibrosis when it is used for a long period of time. Ursodeoxycholic acid and antioxidants such as vitamin E are supposed to have a protective role in preventing chemotherapy-induced liver damage. The aim of this study was to assess the efficacy of these agents in protection against liver injury in pediatric patients with acute lymphoblastic leukemia (ALL).

Methods: Eighty children with ALL were randomly divided into 4 groups: Group 1 used vitamin E 400 mg/d, Group 2 used ursodeoxycholic acid 15 mg/kg/d, Group 3 took a combination of the 2 drugs, while Group 4 served as the control group. CBC, LFT, and liver FibroScan were requested and the results were compared.

Results: Patients who were taking vitamin E showed a mild increase in their total bilirubin compared to the baseline level during the study ($P=0.036$). Mean WBC and absolute neutrophil count increased 6 months after the cessation of the drug compared to the mean values during the study ($P=0.015$ and $P=0.034$, respectively). Those taking ursodeoxycholic acid showed a decreasing trend in the levels of AST and ALT during the study and even 6 months after discontinuing the drug, but the changes were not statistically significant ($P=0.051$ and $P=0.083$, respectively). None of the patients showed evidence of significant fibrosis on their liver FibroScan.

Conclusion: Low-dose methotrexate did not cause significant liver fibrosis in our pediatric leukemia patients. Ursodeoxycholic acid and vitamin E had a minimal role in hepatoprotection among these patients. Larger studies are required to elucidate the beneficial role of these antioxidants.

Keywords • Vitamin E • Ursodeoxycholic acid • Leukemia • Methotrexate • Hepatotoxicity

Evaluation of the Antitumor Activity of *Satureja bachtiarica* Extracts on Lymphoid and Myeloid Leukemia Cells

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Abstract

Background: Plants have a long history in the treatment of cancer. In this study, the effects of different extracts of the *Satureja bachtiarica* plant, which is native to Iran, on the induction of apoptosis and cell differentiation were investigated.

Methods: Techniques used were MTT assay, annexin V/propidium (PI), and cell cycle analysis by flow cytometry and colorimetric assay for caspase-3. Retinoic acid, as a differentiation-inducing compound, was used as the control. The cells were examined by nitroblue dye test, morphology, and CD11b expression.

Results: *S. bachtiarica* extracts showed growth inhibitory effects on K562 and Jurkat leukemia cells, among which 2 hexane and dichloromethane extracts with IC_{50} values less than 50 $\mu\text{g}/\text{mL}$ were the most effective. In annexin V/PI flow cytometry, the hexane and dichloromethane extracts induced 50 to 90% of the cells to undergo apoptosis. Cell cycle analysis showed an increased accumulation of cells in sub-G1 and G0-G1 arrest in the cells treated with 50 $\mu\text{g}/\text{mL}$ of both extracts ($P < 0.001$). An increased caspase 3 activity was seen in the Jurkat cells treated with the hexane and dichloromethane extracts of this plant. The differentiation tests using retinoic acid on NB4 myeloid leukemia cells were set up. The hexane extract was able to significantly induce apoptosis at concentrations of 25 to 50 $\mu\text{g}/\text{mL}$ 72 hours after treatment, but did not induce cell differentiation in these cells.

Conclusion: The extracts of *S. bachtiarica* had growth inhibitory effects due to apoptotic effects on leukemia cells. Therefore, they might be good candidates for the identification of the constituents and the possible in vivo therapeutic effects.

Keywords • Apoptosis • Differentiation • *Satureja bachtiarica* • Leukemia

Effects of Hypoxia on the Promoter Methylation of Apoptosis- and Drug Resistance-Related Genes of a Human Leukemia T-Cell Line Co-Cultured with Bone Marrow Mesenchymal Stem Cells

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Abstract

Background: A well-studied epigenetic mechanism that regulates the gene expression pattern in cells is DNA methylation. Various factors of the bone marrow microenvironment such as mesenchymal stem cells (MSCs) and its hypoxic condition can affect the *in-vivo* and *in-vitro* biology of leukemic cells. We, therefore, we sought to evaluate the effects of hypoxia and MSCs on the promoter methylation status of the BAX, BCL2, and MDR1 genes.

Methods: The MOLT-4 cells were co-cultured with MSCs and treated with CoCl₂ for 6, 12, and 24 hours. Total DNA extraction was done using a DNA extraction kit, and sodium bisulfite treatment was performed on the extracted DNA. To evaluate the methylation status of the nominated gene promoter region, we employed the MSP test.

Results: The promoter regions of the BAX and BCL2 genes of the untreated MOLT-4 cells were in partial methylated and fully unmethylated status, respectively. Furthermore, the MDR1 gene promoter was also in unmethylated mode. This condition showed no change under the effects of hypoxia and co-culture with MSCs.

Conclusion: The methylation levels of the selected gene promoters were not affected by hypoxia and MSCs. Thus, DNA methylation probably is not the key mechanism of the regulation of these gene expressions, where MOLT-4 cells are affected by CoCl₂-induced hypoxia and MSCs. As a final point, such investigations have a chief role in providing novel insights into uncovering the exact mechanisms involved in gene expression controlling.

Keywords • Acute lymphoblastic leukemia • Mesenchymal stem cell • Hypoxia • Epigenetic • Methylation

Evaluation of CEBPA and RUNX-1 Expressions in Patients with

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Abstract

Background: The CCAAT/enhancer binding protein (C/EBP) alpha (CEBPA) and Runt-related transcription factor 1 (RUNX-1) genes have been traditionally regarded as 2 essential genes involved in normal myeloid maturation. Although the link between mutations in these genes and the development of acute myeloid leukemia (AML) has been extensively documented, the ramifications of the gene expression dysregulations of CEBPA and RUNX-1 hasve drawn less attention.

Methods: The present study investigated CEBPA and RUNX-1 gene expression levels in 96 primary AML specimens against a normal control group via real-time RT-PCR.

Results: The results revealed that CEBPA and RUNX-1 gene expression levels were unexpectedly and significantly higher in patients with AML than the levels detected in the normal control group ($P < 0.0001$). Furthermore, the correlation between CEBPA and RUNX-1 was significant and positive ($P = 0.011$ and $r = 0.257$).

Conclusion: Our data contradict the widely established role of CEBPA and RUNX-1 in myeloid differentiation as we had foreseen that lower levels of CEBPA and RUNX-1 expression would be exhibited in patients with AML. This overexpression was accompanied by a conversion of the role of genes involved in myeloid maturation to oncogenes as our data demonstrated that higher levels of CEBPA and RUNX-1 expression were closely correlated with reduced myeloid maturation. It suggests that despite the current established functions of genes involved in cell differentiation, the leukemogenesis process has the capability to transform normal hematopoietic precursors in a manner that may employ the differentiation-related gene at the service of malignancy.

Keywords • Acute myeloid leukemia (AML) • CEBPA • RUNX-1 • Oncogene • Malignancy

Hematological and Clinical Characteristics of Patients with Polycythemia in Shiraz

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Abstract

Background: Polycythemia is divided into three types, namely polycythemia vera, secondary polycythemia, and relative polycythemia. Secondary polycythemia is mainly due to the increase in erythropoietin in patients with low oxygen level caused by pulmonary disease or erythropoietin-producing tumor. Relative polycythemia is caused by obesity and anxiety.

Methods: A total of 58 patients who referred to Hematology Clinic in Shiraz (Iran) were evaluated. Complete blood count and careful physical examination for signs and symptoms of polycythemia, including splenomegaly, hypertension, and a history of thrombosis were performed. JAK2 mutation for the confirmation of polycythemia vera was carried out and the type of smoking was delineated.

Results: Among the 58 patients (37 male and 21 female), 33 patients had polycythemia vera, 20 patients had the secondary type, and 5 had relative polycythemia. The mean age was 52.22 ± 15.94 , mean Hb: 18.26 ± 2.30 , and mean Hct: 55.18 ± 6.25 . The difference in the mean of WBC count, MCH, MCHC, and platelet count was statistically significant; P values of 0.002, 0.006, 0.001, and 0.0005, respectively. These are the means that in polycythemia vera mean WBC count, MCH and platelet count were higher. Patients with secondary polycythemia had a lower platelet count, especially in patients that used a water pipe. Hypertension was more prevalent in the polycythemia vera group (24.24%) and 20% in secondary polycythemia. JAK2 mutation was only positive in the polycythemia vera group (60.5%). In addition, thrombosis was more prevalent in polycythemia vera (15.15%) in comparison with the secondary polycythemia (15%).

Conclusion: Patients with the secondary type of polycythemia have higher Hb and Hct levels, and lower WBC and platelet count. Significant mild thrombocytopenia below 150,000 was seen in patients that used a water pipe. Hypertension and thrombosis were more significant in polycythemia vera.

Keywords • Polycythemia vera • Secondary polycythemia • Thrombosis

Co-Overexpression of Nuclear Factor Erythroid 2-Related Factor 2 and Hypoxia-Inducible Factor-1Alpha Can Enhance Function, Resistance, and Cytokine Production in Human Mesenchymal Stem Cells

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Abstract

Background: One of the most important factors in determining the success of bone marrow transplantation is the number of hematopoietic stem cells (HSCs) in an efficient stromal context. Therefore, co-transplantation of reasonably functional mesenchymal stem cells (MSCs) can greatly improve the outcome of transplantations. Nuclear factor erythroid 2-related factor 2 (NRF2) and hypoxia-inducible factor-1alpha (HIF-1 α) are the most important genes in the body. We assumed that these genes might change the efficiency of MSCs by affecting the production of some cytokines. To address this issue, we manipulated human MSCs to over-express NRF2 and HIF-1 α genes, in this study.

Method: Full-length cDNAs of human NRF2 and HIF-1 α were inserted into human bone marrow MSCs by pcDNA3.1 vector, and the effects of this co-overexpression on the production of some hematopoietic growth factors were investigated. In the co-culture of NRF2 and HIF-1 α over-expressing MSCs with HSCs, the effects of expression on the HSCs were also evaluated.

Results: Co-overexpression of NRF2 and HIF-1 α in MSCs increased the production of stem cell factor and glutathione in the culture media. In the co-culture of NRF2 and HIF-1 α over-expressing MSCs with HSCs, enhancement of colony formation and reduced differentiation of HSCs were observed.

Conclusion: Co-Over-expression of NRF2 and HIF-1 α in human MSCs can augment the production of some hematopoietic growth factors and also antioxidant agents, highlighting a rather effective role of MSCs in cell therapy, especially in bone marrow transplantation.

Keywords • Co-overexpression • Nuclear factor erythroid 2-related factor 2 • Hypoxia-inducible factor • Mesenchymal stem cells

The Effect of Jurkat Cell Culture in Microfluidic System on the Expression of CXCR4 Gene

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Abstract

Background: The expressions of chemokine and receptor genes have been studied in the past. The expression of SDF-1 chemokine and CXCR4 receptor has been considered in embryonic cells, precursor, blood, and cancer due to growth potential, cell migration, activation of transcription, and translation of some genes.

Methods: Initially, microfluidic system was connected to a pump containing RPMI-1640 culture medium with 0.1 ml per hour speed. Then, Jurkat cells were inoculated in the system. The continuous flow incubation of culture medium was constantly dealing with canal cells. Meanwhile, the cells were cultured in flasks. The gene expression was measured using the real-time PCR technique.

Results: The expression of CXCR4 gene in Jurkat cell lines increased in microfluidic systems compared to the conventional cell culture, while this system had no negative effect on cell viability.

Conclusion: Microfluidic system could have the same condition for cell proliferation and production of products due to dynamic conditions and continuous flow of food material and waste removal in the body. Based on CXCR4/SDF-1 receptor and its ligand in cellular migration and homing, the expression of CXCR4 chemokine receptor on cells and the ability to migrate and implant increases for clinical use. This could be a strategy to increase cell potentials for cell therapy. Secretion of SDF-1 chemokine into the damaged section would cause stem cells to repair the inflamed and damaged tissues directly.

Keywords • CXCL12 • CXCR4 • Jurkat cells • Stem cells • Microfluidics

Expansion of CD133+ Hematopoietic Stem Cells Using COPREXA

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Abstract

Background: Hematopoietic stem cell (HSC) transplantation is a highly effective treatment for hematologic malignancies and bone marrow inconsistencies. Restriction of the use of HSCs from the umbilical cord blood (UCB) is due to the low number of HSCs. Therefore, HSC expansion systems in *ex vivo* conditions are intended to overcome this problem. Studies on the cellular copper content in *ex vivo* cultures have proved that increasing levels of copper lead to increased cell maturation, while copper deficiency reduces cell differentiation and thus enhances proliferation. In this study, we used COPREXA, as an FDA-approved copper chelator, to investigate the expansion rate of HSCs.

Methods: CD133+ HSCs were isolated using MidiMACS magnetic separation system from the UCB. Enriched CD133+ cells were cultured in StemLine II serum-free media, consisting of TPO, SCF, Flt3L, and various concentrations of COPREXA (0.2, 1, and 5 μ M). In order to evaluate the expansion of the HSCs, we performed cell counting and CD133 expression by flowcytometry on day 7 post-treatment. The data were analyzed using the Mann–Whitney *U* test with SPSS, version 22.0.

Results: The results of flowcytometry for CD133 at day 7 were as follows: 58.2%, 62.4%, 61.2%, and 41.2% for 0.2, 1, and 5 μ M of COPREXA and the control group, respectively ($P < 0.05$). Cell proliferation at the best concentration (1 μ M) was 5.9-fold higher than that in the control ($P < 0.05$).

Conclusion: The results indicated that the culture of HSCs in the presence of an FDA-approved copper-chelating agent (COPREXA; ammonium tetrathiomolybdate) was able to increase the expansion rate of HSCs. Therefore, hopefully, this strategy could be useful for HSC expansion and improving transplantation.

Keywords • Hematopoietic stem cell • Umbilical cord blood • Copper chelator • COPREXA • Ammonium tetrathiomolybdate • CD133

The Angiogenic Factors Expression Profile of K562 Cell Line in Co-Culture with Bone Marrow Derived-Mesenchymal Stem Cells

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Abstract

Background: Angiogenesis, the process of new blood vessel formation, is essential for solid tumor development. Since acute myeloid leukemia (AML), known as a liquid tumor, it was believed that angiogenesis is not implicated in its development. Mesenchymal stem cells (MSCs), key elements of the tumor microenvironment, play an important role in solid tumor development by the induction of angiogenesis. However, there is little information about their role in liquid tumor angiogenesis. Erythroid leukemia is an unusual form of AML, which is accompanied by poor prognosis. The present study aimed to investigate the effect of bone marrow-derived MSCs on the angiogenic activity of K562 cells, which are erythroid leukemia cell line.

Methods: K562 cells were co-cultured with bone marrow derived-MSCs. After 8, 16 and 24 hours, alterations in the expression of 8 chemokine genes involved in angiogenesis were evaluated by quantitative real-time polymerase chain reaction (qRT PCR). Mono-cultures of K562 cells were used as the control.

Results: We observed that in the K562 cells co-cultured with bone marrow derived-MSCs, there was a significant increase in CXCL3 gene expression ($P < 0.01$); it is a pro-angiogenic gene.

Conclusion: Our observations have demonstrated that bone marrow-derived MSCs are able to promote the expression of chemokine gene involved in angiogenesis in K562 cells. Therefore, poor prognosis of erythroid leukemia may be related to the effect of MSCs as one of the key environmental elements in the bone marrow. Hence, in this disease, therapeutic strategies that modify angiogenesis may be beneficial in improving patient's clinical status.

Keywords • Mesenchymal stem cells • Angiogenesis • Erythroid leukemia • Chemokine

Gene-Modified Mesenchymal Stem Cells (AD-MSCs) against Leukemia

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Abstract

Background: Mesenchymal stem cells (MSCs) are a group of adult stem cells naturally found in the body. MSCs have attracted considerable attention in the fields of cell and gene therapy due to their intrinsic characteristics and ability to differentiate into multiple lineages. Whereas the bone marrow has been the 1st recognized source of MSCs, the adipose tissue represents a valid source of mesenchymal progenitors. Adipose-derived mesenchymal stem cells (AD-MSCs) may offer efficient tools for cell-based gene therapy approaches.

Methods: In this study, we evaluated whether AD-MSCs could deliver pro-apoptotic molecules for the treatment of leukemic cells. Human AD-MSCs were transduced with a lentiviral vector encoding secretory tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), a proapoptotic ligand that induces apoptosis in a variety of human cancers but not normal tissues. TRAIL AD-MSCs could serve as constant source of TRAIL production and delivery. AD-MSCs engineered with TRAIL targeted HL-60 cells and AML-M3 mononuclear cells (MNCs).

Results: We observed significant apoptosis-inducing potential by TRAIL AD-MSCs in HL-60 cells and AML-M3 patients' MNCs compared to the control group ($P < 0.05$). *In-vitro* co-culture migration assays on trans-well plates showed that the HL-60 cells culture, but not the FBS-free medium, supported the migration of the MSCs and enhanced their migration ($P < 0.05$).

Conclusion: This treatment modality failed to completely induce cell death in all HL-60 or MNCs; nevertheless, it indicated the need for finding co-treatments appropriate to the type of resistance mechanism. Further, these results suggest that human AD-MSCs have potential use as effective delivery vehicles for therapeutic genes in the treatment of bone marrow cancers.

Keywords • Mesenchymal stem cell • Apoptosis • HL-60 cells • TRAIL • Adipose tissue

The Role of Hemovigilance to Improve Patient Safety: Challenges and Tools

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Abstract

Hemovigilance is defined as a set of surveillance procedures covering the entire blood transfusion chain from blood donation, collection, and processing into blood components, as well as the follow-up of blood recipients. It includes all information about the monitoring, reporting, investigation, and analysis of unexpected or undesirable events and near misses related to the blood donation, processing, transfusion, and taking action to prevent their occurrence or recurrence. The reporting systems play a fundamental role in enhancing patient safety by learning from failures, putting in place system changes to prevent repetition in future, and to improve the safety of blood transfusion.

The hemovigilance system should involve all relevant stakeholders and coordinate between the blood transfusion service, clinical staff, blood banks, and transfusion committees of a hospital. The resulting modifications to transfusion policies, standards, and guidelines, as well as improvements to processes in blood services and transfusion practices in hospitals, lead to improved patient safety. The scope of different hemovigilance systems varies due to differences in the spectrum of reporting, i.e. reporting of all or only severe adverse reactions.

Hemovigilance starts from attracting, recruiting blood donor, precise indication, and correct administration. All professionals involved in prescribing and administering blood products must be trained to identify and manage adverse reactions and to establish measures to prevent future incidents and to minimize risk.

Keywords • Blood transfusion • Blood donors • Hemovigilance
• Adverse transfusion reaction • Blood safety

SFRP1 and SFRP2 Genes Promoter Methylation Status in CML Patients

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Abstract

Background: Chronic myeloid leukemia (CML) is a myeloproliferative disease characterized by an increase in myeloid, erythroid, and megakaryocyte series in the bone marrow and peripheral blood. Secreted frizzled-related protein (SFRP) is an important inhibitor of the Wnt signaling pathway in healthy subjects. Aberrant regulation of the Wnt signaling pathway is a common factor in cancer biology, and methylation of the SFRP gene promoter leads to uncontrolled cell proliferation in cancer. CML was the 1st disease in which the role of the Wnt signaling pathway was described. In the present study, methylation status of the SFRP1 and SFRP2 genes was determined in newly diagnosed CML patients as well as healthy subjects.

Methods: Methylation status of the SFRP1 and SFRP2 genes was studied in the peripheral blood samples of 33 CML patients at diagnosis as well as 25 healthy subjects as controls. Methylation-specific polymerase chain reaction was used to check the methylation status of the SFRP1 and SFRP2 genes. The Mann—Whitney test was applied to determine the correlation between the hypermethylation of the SFRP1 and SFRP2 genes and clinical criteria.

Results: The results showed 16.1% and 27.2% hypermethylation of the promoters of the SFRP1 and SFRP2 genes, respectively, but methylation was not shown in any of the control samples.

Conclusion: Like other leukemias and solid tissue neoplasias, methylation of the SFRP1 and SFRP2 genes is observed in CML patients. The methylation of these genes is, thus, likely to be involved in the onset of this disease.

Keywords • Neoplasms • Leukemia • Methylation

Evaluation of Genomic Interactions between Two Quantitative Trait Loci and Their Efficacy in Gamma-Globin Expression in Beta-thalassemia Intermedia Patients

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Abstract

Background: Globin switching and expression are significant factors as regards blood hemoglobin levels and are effective on the phenotype of some hemoglobinopathies such as thalassemia. Molecular mechanisms of globin switching are not identifiable; however, several quantitative trait loci and polymorphisms on chromosomes 2p, 6q, 8q, and X account for variations in the fetal globin expression level. Increased HbF levels lead to a compensation of a low HbA level, which results in improving the phenotype in some thalassemia intermedia patients.

Methods: We studied the effects of the interaction between a region on intron 6 of the thymocyte selection-associated high mobility group box (TOX) gene on chromosome 8q and the XmnI locus on the gamma-globin promoter on chromosome 11p. Fetal globin expression was evaluated in 150 thalassemia intermedia patients analyzed by direct DNA sequencing for the TOX gene and the RFLP method for the XmnI locus.

Results: Our results showed a significant interaction between 1 quantitative trait locus on intron 6 of the TOX gene (rs9693712) and the XmnI locus on gamma-globin expression.

Conclusion: Our study shows that interchromosomal interactions mediate through transcriptional machinery to preserve true genome architectural features, chromosome localization in the nucleus, and DNA bending. These interactions can be a part of the unknown molecular mechanism of globin switching and the regulation of gene expression.

Keywords • Chromosome 8q • QTL • Globin gene • HbF • Thalassemia intermedia

The First Report of Thalassemia Registry, Thalassemia Research Center, Mazandaran University of Medical Sciences, Iran, 2016

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Abstract

Background: This is the 1st report of the electronic registry of patients with beta-thalassemia major residing in Mazandaran Province.

Methods: An electronic registry (www.thr.mazums.ac.ir) was designed in TRC. Patients with a definitive diagnosis of beta-thalassemia major under management in 14 hospital-based thalassemia clinics and wards affiliated with Mazandaran University of Medical Sciences were included. A nurse was trained to enter that data in each hospital. Social, epidemiologic, clinical, and laboratory characteristics of the patients were entered in the software. Descriptive statistics were used to summarize the data.

Results: This report consisted of almost half of the known patients. Totally, 1,053 patients, including 553 (52.2%) females, at a mean age of 30 ± 8.9 years were registered by the 14 centers. A total of 920 (87.4%) patients were transfusion-dependent. The level of formal education was beyond the high school degree in almost 30%. Additionally, 571 (54.2%) patients were single and 350 (33.2%) patients had jobs. Splenectomy was performed for 606 (58%) patients. Diabetes mellitus, hypoparathyroidism, and hypothyroidism were diagnosed in at least 12%, 14.3%, and 11%, respectively. At least 11.2% had cardiomyopathy; however, special cardiac assessment was missing in many records. The most popular iron chelator medication was desferrioxamine, which was used alone (50.4%) or in combination with deferiprone (24.3%).

Conclusion: This registry is not only a good source for epidemiological research but also a tool for encouraging better management for this group of patients.

Keywords • Thalassemia major • Registries • Epidemiology • Iron chelating agents

CC Chemokines CCL2, CCL3, and CCL5 Are Differentially Expressed in the Serum of Patients Suffering from Sickle-Cell Disease and Carriers

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Abstract

Background: Sickle-cell hemoglobinopathies are a group of genetic disorders caused by a single base-pair DNA mutation at the hemoglobin beta chain. Chemo/cytokine networks play a fundamental part in the pathogenesis of inflammatory and infectious diseases. They are also involved in balancing the angiogenesis/angiostasis processes to form new vessels. We aimed to measure the circulating levels of CC chemokines CCL2, CCL3, and CCL5 in the plasma of sickle-cell disease (SCD) patients.

Methods: The present cross-sectional study was performed at the Kerman Special Disease Center and Rafsanjan Molecular Medicine Research Center between 2015 and 2016. Samples were collected from 77 children with SCD and 70 controls. Serum was separated from each patient and CCL2, CCL3, and CCL5 were measured using ELISA.

Results: The findings of this study demonstrated that the serum concentrations of CCL2 and CCL3 were elevated in the SCD patients when compared with the controls. The results also showed that the circulating levels of CCL5 were decreased in the SCD patients in comparison to the control subjects. However, we found increased levels of CC chemokines in the SCD patients suffering from pain crisis, but the difference was not significant.

Conclusion: In light of the results of this study, we can speculate that CC chemokines are important predictive factors for the initiation of complications in SCD patients. The elevated level of pro-inflammatory CC chemokines may also be related to inflammatory responses associated with SCD complications.

Keywords • Sickle-cell disease • Chemokine CCL2 • Chemokine CCL3 • Chemokine CCL5

The Relationship between Gene Expression and the Level of Erythroferrone in Patients with β -Thalassemia Major

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Abstract

Background: Ineffective erythropoiesis and chronic anemia caused by β -thalassemia major are the results of iron overload by both blood transfusion and increased iron absorption level through iron-regulatory hormone hepcidin suppression. Being an erythropoiesis-driven regulator of iron homeostasis, erythroferrone (ERFE) mediates the suppression of the iron-regulatory hormone hepcidin in order to increase iron absorption and consequently the mobilization of iron from stores. The present study aimed to examine the relationship between gene expression and the level of erythroferrone in patients with β -thalassemia major.

Methods: The quantity of gene expression, erythroferrone, and hepcidin proteins were measured in β -thalassemia patients, before and after blood transfusion, using real-time-PCR and ELISA techniques and compared with the amount of iron and ferritin in sera.

Results: Erythroferrone causes hepcidin suppression and leads to increased iron absorption. Hence, it seems that blood transfusion causes reduction in the amount of erythroblasts in the bone marrow and peripheral blood. As a result, erythroferrone production declines, which increases the hepcidin gene expression and reduce the iron absorption.

Conclusion: The goal of this study was to understand the potential of erythroferrone in prognosis and clinical therapeutic applications. It seems that, in the near future, erythroferrone can potentially be considered as a therapeutic target for treating iron overload in major β -thalassemia patients.

Keywords • β -thalassemia major • Erythroferrone • Hepcidin • Real-time PCR • Gene expression • Iron overload

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Explaining the Beliefs in Patients with Sickle-Cell Anemia

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Abstract

Background: Sickle-cell anemia is the most common form of inherited blood disorder and is caused by a genetic mutation that leads to the production of abnormal hemoglobin molecules and eventually defective hemoglobin in red blood cells. This disease causes spirituality instability and lack of faith among patients and leads to contradictions in their beliefs. The present study was carried out to examine the experience of spirituality instability among patients with this disease.

Methods: This study was conducted based on the phenomenological qualitative approach. The study population comprised 11 patients with sickle-cell anemia in Kohgiluyeh and Boyerahmad Province. Sampling was purposive, and data were collected using unstructured interviews. Colaizzi's 7-stage method was employed for analyzing the data.

Results: All the participants in the study reported that the disease had made them closer or farther from God, especially at the time of the recurrence of the disease. Ninety-two codes at the 1st level and 2 codes at the 2nd level were extracted from the interviews, which included instability of faith and attention to the beliefs; these 2 categories formed the original concept of "beliefs".

Conclusion: According to the participants, they had contradictory beliefs that varied according to the condition of their disease and in different situations. Sometimes they found solace by saying prayers and reading the Quran, while at times they grew so bored and aggressive that they would show profanity. It is recommended to run programs to pacify the soul and body of patients. One such method can be spiritual tranquility.

Keywords • Sickle-cell anemia • Phenomenology • Belief

Determination of the Plasma Concentration of Protein Z(ZP) and Protein Z-Dependent Protease Inhibitor (ZPI) in Beta-Thalassemia Major Patients and Healthy Controls

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Abstract

Background: Thalassemia is the most common congenital hemolytic disorder in Iran. It is caused by partial or complete deficiency in globin chain synthesis. Homozygous carriers of beta-globin gene defects suffer from severe anemia and other serious complications from early childhood. Thalassemia patients have a higher risk for thromboembolic events. Recent investigations have suggested a correlation between protein Z (ZP) and protein Z-related protease inhibitor (ZPI) deficiency and thrombosis. Thus, the aim of this study was to evaluate ZP and ZPI levels in beta-thalassemia patients and healthy controls.

Methods: In this case-control study, we recruited 40 patients with thalassemia major (cases) and 40 healthy subjects as controls, who were selected from Gachsaran Rajaei Hospital. ZP and ZPI were measured via the sandwich ELISA technique. The results were analyzed by SPSS, version 16, using the Student *t*-test and the Mann-Whitney test. A P value less than 0.05 was considered statistically significant.

Results: ZP and ZPI were significantly higher in the thalassemic patients than in the healthy controls ($P=0.004$ and $P<0.001$, respectively). Also, the ZP levels were significantly higher in the splenectomized thalassemic patients than in the non-splenectomized ones ($P=0.015$), while there was no significant difference in the ZPI levels between the non-splenectomized and splenectomized patients.

Conclusion: Reduced ZP and ZPI levels exerted no impact on hypercoagulable state in our thalassemia major patients. It seems that the elevation in ZP and ZPI in thalassemia patients, especially in splenectomized patients, is caused by inflammation.

Keywords • Thalassemia major • Thromboembolic events • ZP • ZPI

Survival Rate in Thalassemia Major Patients: Difference between Date of Diagnosis and Date of Birth as an Index Date for Calculating Follow-Up

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Abstract

Background: This study aimed to identify the effects of the delayed diagnosis of thalassemia on the survival rate among thalassemia major (TM) patients.

Methods: A retrospective cohort study was conducted on 704 Iranian TM patients in 2016. The survival rates were calculated by delay in diagnosis status (no delay or delay in diagnosis). The Log-rank test of differences in Kaplan–Meier survival curves was used for the category of delayed diagnosis in the patients.

Results: In this TM cohort, 192 patients died. Delayed diagnosis was observed in 460 (65.3%) of the TM patients. We found a significant difference between the survival rates of the patients with and without delay in diagnosis ($P=0.027$). We also calculated the attributable fraction among the patients with delay in diagnosis and found that about 25% of the thalassemia-related deaths among the patients with delayed diagnosis could be attributed to delay in diagnosis. In other words, if delay in diagnosis had not occurred, about 25% of the thalassemia-related deaths could have been avoided.

Conclusion: Delay in TM diagnosis, as an independent factor, might have impact on the mortality rates of TM patients. Improvement of community education and also reduction of screening test errors may reduce the incidence.

Keywords • Delayed diagnosis • Thalassemia • Survival rate

Hemoglobin Arya: A Case Report

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Abstract

Background: A hemoglobin variant (hemoglobin Arya) is described from an Iranian female. The substitution is at residue 47 (CD5) of the alpha chain in which aspartic acid has been substituted by asparagine.

Methods: A retrospective study during summer 2016 was performed in the reference laboratory of Kermanshah (Iran). The capillary electrophoresis and CBC were done.

Results: There were two patients with Arya hemoglobin. The first patient (case 1) was a 59-year-old woman with the thalamic feature of RBC index; Hb A2: 6.3, Hb F: 1.3, Hb Arya: 12.6, and Arya A2 variant: 0.9. The second patient (case 2) was a 36-year-old woman with the thalamic feature of RBC index; Hb A2: 5.4, Hb F: 2.3, Hb Arya: 11.8, and Arya A2 variant: 0.8.

Conclusion: The presence of hemoglobin Arya was not associated with clinical symptoms. This variant has normal stability at 50°C, but is slightly unstable when tested at 55°C.

Keywords • Hemoglobinopathy • Hemoglobin arya • Kermanshah • Electrophoresis

Hemoglobin J-Homozygote: A Case Report

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Abstract

Background: Substitution at ($\beta 77$ His \rightarrow Asp) leads to a higher negative charge of the β J-Iran subunit, which enhances its electrostatic attraction for the normally positively charged α subunit. Therefore, more Hb J-Iran than Hb A forms in the red blood cells of heterozygotes.

Case Presentation: Herein, the case of a man with Hb J-Iran confirmed by electrophoresis is reported. The patient was a 45-year-old man from Kermanshah (Iran) with the thalamic feature of RBC indexes; with low hemoglobin and high RBC count, microcytosis, and hypochromic RBC. A complete blood count (CBC) with capillary electrophoresis was performed. The capillary electrophoresis showed Hb J 91.4% and Hb A2 4.9%.

Conclusion: Since there are two genes for β -globin, an individual heterozygous for a β -globin variant would be expected to have equal proportions of normal and abnormal hemoglobin levels. Differences between the normal and other variant hemoglobin levels reflect the different tendencies of variants that assemble with normal alpha subunits.

Keywords • Beta-globin • Hemoglobin J • Kermanshah • Electrophoresis

Experiences of Patients with Sickle-Cell Disease in Kohgiluyeh and Boyerahmad Province

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Abstract

Background: Sickle-cell anemia is the most prevalent form of hereditary dysentery in the world. It is diagnosed by repeated painful crises. Sickle-cell anemia creates many physical, mental, and spiritual side effects. An understanding of how these patients experience this disease is very important in providing accurate description and concepts of their problems. The purpose of this study was to describe the experiences of patients with sickle-cell anemia.

Methods: This research was performed by using the phenomenology method, which is a qualitative approach. The study population consisted of 11 patients with sickle-cell anemia in Kohgiluyeh and Boyerahmad Province. Sampling was purposive, and Colaizzi's method was used for data analysis.

Results: The results of this research were categorized to 253 first-level coding, 25 second-level coding, and 7 main themes, comprising: 1) pain, 2) requirements, 3) issues and challenges, 4) self-care deficits, 5) beliefs, 6) attitude of society, and 7) side effects, all of which showed the general structure of the experiences of the patients with sickle-cell anemia.

Conclusion: Patients with sickle-cell anemia have many requirements in order to be able to improve their life quality. Furthermore, self-care deficits, society's attitude, and the side effects of this disease create a large number of problems for this group of patients.

Keywords • Sickle-cell anemia • Patients • Experiences • Phenomenology

Explaining the Complications Associated with Sickle-Cell Anemia

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Abstract

Background: Sickle-cell anemia is the most common form of inherited blood disorder and is caused by a genetic mutation that leads to the production of abnormal hemoglobin molecules and eventually defective hemoglobin in red blood cells. It is associated with many problems for patients and their families. Numerous unpredictable and astringent complications that occur with this disease render the lives of this group of patient harder. Therefore, we sought to evaluate the experience of complications associated with this disease.

Method: This study was conducted based on the phenomenological qualitative approach. The study population encompassed 11 patients with sickle-cell anemia in Kohgiluyeh and Boyerahmad Province. Sampling was purposive, and data were collected using unstructured interviews, Colaizzi's 7-stage method was employed for data analysis.

Results: All the participants complained of the complications of the disease. Totally, 138 participants were coded as 1st level and 11 as 2nd level, which comprised economic problems, physical and motor problems, psychological pressure, vascular access problems, infections and colds, outcomes, difficulties caused by the disease, barriers to education, sleep problems, dependence and addictive complications, and invasive procedures, all of which were extracted from the interviews. All these composed the original concept of "complications associated with the disease".

Conclusion: The participants in the current study complained of the complications associated with the disease, causing them a large number of psychological, physical, economic, and social problems. It is recommended that policies be based on support and meeting the needs of this group of patients and improving their quality of life.

Keywords • Sickle-cell anemia • Phenomenology • Complication

Hemoglobin Setif Incidence in a Sample Population of Kermanshah Reference Laboratory in Iran

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Abstract

Background: Hemoglobin Setif is a rare type of hemoglobinopathy resulting from a point mutation at codon 94 (GAC>TAC) of the $\alpha 2$ -globin gene and an aspartic acid to tyrosine substitution.

Methods: In manual and automated hemoglobin (Hb) electrophoresis examination of the case, an unusual band was detected and the result of subsequent capillary electrophoresis suggested being Hb Setif.

Results: Among 852 hemoglobin analysis performed within 3 months, there was 0.82% hemoglobin Setif that included 4 men and 3 women.

Conclusion: Hemoglobin Setif produces pseudo-sickling of red cells in vitro; the nature of the process and the conditions that trigger it are unknown. Studies of red cells, hemolysates, purified hemoglobin solutions, and artificial mixtures of Hb A and Setif suggest that pseudo-sickling is produced by intracellular crystallization of insoluble hemoglobin. Increased tonicity of the suspending medium accentuates the process, probably by causing a rise in intracellular hemoglobin concentration. If precipitates from A/Setif mixtures are analyzed, they always contain Hb A, suggesting an unusual mechanism for the process. Despite the fact that osmolality in the renal medulla is similar to that producing pseudo-sickling in vitro, carriers do not have renal dysfunction of the type found in patients with sickle cell disease.

Keywords • Hemoglobinopathy • Hb setif • Kermanshah • $\alpha 2$ -globin

Hemoglobin J Heterozygote: A Case Report

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Abstract

Background: The β^{77} His \rightarrow Asp substitution leads to a higher negative charge of the β J-Iran subunit, which enhances its electrostatic attraction for the normally positively charged α subunit. Therefore, more Hb J-Iran than Hb A forms in the red blood cells of heterozygotes.

Methods: A retrospective study during the first 6 months of 2016 was performed in the Reference Laboratory of Kermanshah (Iran). The capillary electrophoresis and CBC were done.

Results: There were two patients with Hemoglobin J, as confirmed by electrophoresis. The first patient (case 1) was a 9-year-old boy with the normal feature of RBC index, Hb J: 52.0%, Hb A: 45.2%, and Hb A2: 2.4%. The iron profile was normal. The second patient (case 2) was a 31-year-old woman with the normal feature of RBC index, Hb J: 50.6%, Hb A: 46.5%, and Hb A2: 2.5%. The iron profile was normal

Conclusion: Hb J-Iran (β^{77} His \rightarrow Asp) is one of the first hemoglobin variants that have been discovered in Iran. Since there are two genes in β -globin, an individual heterozygous for a β -globin variant would be expected to have equal proportions of normal and abnormal hemoglobins. In heterozygous forms of hemoglobinopathies with the β -variant chain, the normal β chain compared to the abnormal β chain has a greater affinity to combine with α chain and form normal Hb A1. Hence, the amount of Hb A1 is usually greater than abnormal hemoglobin.

Keywords • Beta-globin • Hemoglobin J • Kermanshah • Electrophoresis

Hemoglobin D and Q Incidence in a Sample Population of Kermanshah Reference Laboratory in Iran

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Abstract

Background: Hemoglobinopathies are among the most prevalent genetic disorders worldwide. It occurs as a result of mutations in the gene involved in synthesizing hemoglobin chains. Hemoglobin D (Hb D) is one of these disorders identified by a single nucleotide mutation at codon 121 of beta globin chain. Hb Q is identified by a single nucleotide mutation at codon 75 of alpha globin chain.

Methods: A retrospective laboratory study was conducted during spring-summer 2016 on 1,759 patients in Kermanshah Reference laboratory (Iran). Capillary zone electrophoresis was done to find out Hb D and Q.

Results: The data revealed 1.02% hemoglobin D and 0.56% hemoglobin Q.

Conclusion: The carriers of Hb D and homozygous cases for Hb D were not anemic and had normal red blood cell morphology, as they are not usually detected. Single nucleotide mutations in $\alpha 1$ or $\alpha 2$ genes produce abnormal α -chain hemoglobin. Hb Q disorders, including Hb Q-Iran, Hb Q-Thailand, and Hb Q-India are important Hb variants. All above-mentioned hemoglobins are a slow-moving variant that migrates at the electrophoretic position of Hb S at alkaline PH.

Keywords • Hemoglobin D • Hemoglobin Q • Hemoglobinopathy • Kermanshah

Complementary and Alternative Medicine Use in Thalassemia Patients in Southern Iran

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Abstract

Background: Patients with thalassemia may try other therapies besides their conventional treatments. We sought to determine the frequency and pattern of complementary and alternative medicine (CAM) use in thalassemia patients in south of Iran.

Methods: The survey was done using a validated questionnaire, which was distributed among 122 thalassemia patients or their parents. The patients had referred to an outpatient thalassemia clinic in Shiraz, Southern Iran, for blood transfusion.

Results: From 122 families approached, 108 questionnaires were completed and returned (response rate=88.5%). The mean age of the patients was 22.9 ± 7.9 years (range=4-45 years) with a female/male ratio of 1.84. Seventy-four (68.5%) of the responders used CAM at least once during their life, and about half of them used it concurrently with their conventional treatments. The most reported CAM products and practices were mint juice (50%) and faith healing (50%), respectively. The most common reasons for CAM use were increased general health, appetite and well-being, and improvement of osteoporosis. Children whose parents used CAM were 5.54 times more likely to use CAM ($P < 0.001$, 95% CI: 2.22 to 13.78). The most common information source about CAM was physicians, who were the most trusted source as well. More than 75% of the responders had disclosed using CAM to their physicians.

Conclusion: CAM is frequently used in thalassemia patients to ensure their sense of well-being and help them overcome the complications of their illnesses. Hematologists should be aware of this issue and openly discuss with their patients to help them choose the best options.

Keywords • Complementary medicine • Thalassemia • Hemoglobinopathies

Association of Serum Ferritin level with Insulin Resistance in β -Thalassemia Patients

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Abstract

Background: β -thalassemia is the most common inherited hemoglobinopathy in the world. Oxidative stress and chronic iron overload have important roles in the pathophysiology of thalassemia. The present study aimed to determine the relationship between ferritin level, oxidative stress, and insulin resistance in the β -thalassemia major patients.

Methods: The population consisted of 52 β -thalassemia major patients and 42 healthy controls. The serum level of glucose, insulin, ferritin, albumin and ischemia-modified albumin (IMA) were measured. Beta cell function (HOMA-B%), insulin sensitivity (HOMA-S%), and insulin resistance (HOMA-IR₂) were determined with homeostasis model assessment method2 (HOMA2) calculator.

Results: Serum level of IMA and IMA/albumin ratio, markers of oxidative stress, and serum ferritin level were significantly higher in β -thalassemic patients compared with the control group. Serum ferritin levels had a significant negative ($r=-0.326$, $P<0.05$) and positive ($r=0.388$, $P<0.01$) correlation with HOMA-S% and HOMA-IR₂ respectively. No significant association was observed between oxidative stress and insulin resistance in the patients.

Conclusion: The results of this study suggest that iron overload may lead to insulin resistance in β -thalassemia patients.

Keywords • β -thalassemia • Insulin resistance • Oxidative stress • Ferritin

Fertility Assessment in Thalassemic Men

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Abstract

Background: The causes of male infertility in the general population are multiple while in β -thalassemia are classically considered as the result of iron deposition in the endocrine glands. Adult male patients with β -thalassemia, on frequent blood transfusions, are predisposed to develop acquired hypogonadism. The present study aimed to evaluate the pubertal development and function of the pituitary-testicular axis in adolescent males with β -thalassemia major and intermedia.

Methods: A prospective study was conducted at a teaching hospital in Tehran (Iran) to evaluate testicular volume, semen parameters and serum FSH, LH, and testosterone concentrations in 62 young male patients with major and intermedia thalassemia, aged 18-41 years.

Results: At the time of the study, their serum ferritin levels ranged from 182 to 11,053 ng/mL (mean 2,067 ng/mL). The mean volume of patients' ejaculate was 2.3 cc. The mean concentration of sperm was 61.04 million per milliliter. The mean size of right testis was 11.4 cc and the mean size of left testis was 11.7 cc. Hypogonadism and hypothyroidism were seen in 22.6% and 17.7% of the patients, respectively. The mean level of FSH was 3.7 mIU/ml, LH was 4.6 mIU/ml, and testosterone was 4.8 ng/dl. The mean level of serum ferritin was 2,067 ng/dl.

Conclusion: The results suggest that the concentrations of serum testosterone, LH, and FSH in thalassemic men have a significant correlation with sperm parameters and testicular volume.

Keywords • Beta-thalassemia • Fertility, • Spermatogenesis • Puberty • Hypogonadism

Quality of Life and Depression in Patients with Beta Thalassemia Major

Mahsa Imanian

Abstract

Background: Thalassemia could influence diverse aspects of patients' quality of life and depression. The present study aimed to evaluate the quality of life and depression in patients with thalassemia major.

Methods: Reliable scientific websites were used in the literature review of the present study.

Results: Published studies revealed that patients with beta thalassemia major (BTM) experience considerable limitations in their role performance due to not only physical restrictions, but also emotional problems, reduced energy level, and poor general health. It seems that psychological disorders, such as depression, are common among patients with BTM. It is reported that depression has negatively affected the quality of life in both physical and mental health. The negative impact of depression on the quality of life could be described by its impact on daily functioning, social relationship, productivity, and physical disability. The impact of depression on the quality of life is greater than chronic conditions such as diabetes, hypertension, and chronic lung disease. Our literature review showed that patients might react to thalassemia related distress with maladaptive coping strategies, indicating the feeling of helplessness and hopelessness, future expectations, and perceived social support. Therefore, BTM increases depression and results in negative effects on the physical and mental quality of life.

Conclusion: In addition to medical therapies, psychopathological evaluation and treatment (if indicated) could positively affect the quality of life and depression in BTM patients. Therefore, it is recommended that the treatment of these comorbidities should be taken into account and effective psychotherapeutic interventions addressing emotional problems in thalassemia should be considered.

Keywords • Quality of life • Depression • Beta thalassemia major

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CC Chemokines CCL24 and CCL26 show Increased Expression in Serum of Patients Suffering from Sickle Cell Disease and Carriers

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Abstract

Background: Sickle cell hemoglobinopathies are a group of genetic disorders caused by a single base-pair DNA mutation at the hemoglobin beta chain. Chemo/cytokines network plays a fundamental part in the pathogenesis of inflammatory and infectious diseases. The present study aimed to measure the circulating levels of CC chemokines CCL24 and CCL26 in the plasma of sickle cell patients (SCD).

Methods: The present cross-sectional study was performed at Kerman Special Disease Center (Kerman, Iran) and Rafsanjan Molecular Medicine Research Center (Rafsanjan, Iran) during 2015 to 2016. Samples were collected from 77 children with SCD and 70 controls. Serum separated from each patient and circulating levels of CC chemokines CCL24 and CCL26 were measured using ELISA.

Results: The findings of the present study demonstrated that serum concentrations of CCL24 and CCL26 were elevated in SCD patients when compared with controls. However, we found increased levels of CC chemokines in SCD patients suffering from pain crisis, but the difference was not significant.

Conclusion: Based on the results, we may speculate that CC chemokines are an important predictive factor for the initiation of complications in SCD patients. The elevated level of pro-inflammatory CC chemokines may also be related to inflammatory responses associated with SCD complication.

Keywords • Sickle cell disease • Genetic disorders • CC chemokines • Inflammatory diseases

The effect of Humor as a Nursing Intervention on Depression in Adolescents with Leukemia

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Abstract

Background: As a serious complication of cancer, depression has various effects in different contexts such as mental and physical health, treatment, and disease progression. The present study aimed to determine the effect of humor as a nursing intervention on depression in adolescents with leukemia.

Methods: The present experimental study included the participation of 62 children and adolescents with leukemia in the 12-18 year age group. Demographic and depression in children and adolescents (CADS) questionnaire was used for data collection. The experimental group underwent nursing interventions, based on the use of humor, in the form of 30 minutes weekly sessions for 8 weeks. The control group received the routine care interventions.

Results: A statistically significant difference was not found in demographic variables between the two groups ($P>0.05$). No statistically significant difference was found between the intervention and control groups in pre-test scores ($P>0.05$). After adjusting the pre-test scores, a significant effect of depression between the participants of both groups was obtained ($P<0.001$). The average depression score in the experimental group in pre-test and after the intervention was 36.16 and 18.19, respectively. Paired *t* test showed a significant difference between the scores before and after the intervention ($P<0.0001$).

Conclusions: The results showed that the use of nursing interventions based on humor could greatly reduce depression in children and adolescents with leukemia. It is a recommended health care method in such patients.

Keywords • Humor • Nursing • Depression • Leukemia • Adolescent

Bioinformatics Investigation of miRNAs Involved in the Expression of Notch1, CCND1, and MYC Genes Regulation

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Abstract

Background: MicroRNAs (miRNAs) are small non-coding molecules that are involved in various acts of cell biology. Their roles in various cancers have also been proven. miRNAs act as biomarkers for prognosis, diagnosis, and treatment of cancers; and have attracted a lot of attention. NOTCH is one of the most important signaling pathways that regulates gene expressions and plays a critical role in cell proliferation, differentiation, and apoptosis. Notch1 gene encodes a receptor that interacts with its ligand followed by starting signaling pathway. CCND1 and MYC are the two important downstream genes of NOTCH signaling pathway, which encodes Cyclin-D1 and c-Myc proteins that are proto-oncogenes contributing in cell proliferation, differentiation, and cell cycle.

Methods: miRNA prediction databases including TrgetScan, mirWalk, miRANDA, microRNA, DIANA micro-T, and miRBase were applied to predict miRNAs targeting Notch1, MYC, and CCND1 genes. These algorithms are based on miRNA 3'UTR of mRNA attachment. The results obtained from miRNA prediction databases were categorized based on frequency, free energy, and seed types.

Results: Bioinformatics method prediction showed that miR-34a targets Notch1, MYC, and CCND1 genes; miR-449a targets Notch1 and CCND1 genes; miR-1827 targets MYC; and miR-106b targets CCND1 gene with the highest scores.

Conclusion: MicroRNAs have the potential to be used as biomarkers and targets for the treatment of different cancers. Considering the role of miRNAs in the regulation of gene expression, the application of bioinformatics methods is low-cost and more accessible than other methods (e.g. microarray) and gives useful information about the miRNAs involved in various cancers.

Keywords • Bioinformatics • MicroRNA, • Notch1 • MYC • CCND1

Association between ICH and VEGF in Patients with Severe Factor XIII Deficiency

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Abstract

Background: Congenital factor XIII deficiency (CFXIIID) is a rare form of bleeding. Spontaneous intracerebral hemorrhage (ICH) occurs in up to the one-third of FXIII deficient patients. The occurrence of ICH in this disorder is considered as multifactorial and the pathogenesis of brain injury after ICH is poorly understood. Vascular endothelial growth factor (VEGF) plays important roles in both physiological and pathological neovascularization. The present study aimed to investigate the association between ICH and plasma VEGF levels in patients with severe FXIII deficiency.

Methods: The study was conducted on 20 FXIII-deficient patients with ICH as case and without ICH as the control group. ICH was diagnosed based on CT scan and MRI results. Blood samples were collected in EDTA anticoagulated tubes within 24-48 hours after ICH. The concentration of VEGF in the plasma was measured by ELISA. Data analysis was performed by the SPSS software.

Results: There was no statistically significant difference between age ($P=0.06$) and gender ($P=0.4$) among the study groups. The majority of patients (82.3%) had the bleeding only once and 14.7% had the bleeding twice in their clinical history. Only one patient (3%) had the bleeding history 3 times. The average plasma level of VEGF was higher in patients with ICH than the control group; however, such difference was not statistically significant ($P=0.175$).

Conclusion: The results showed that ICH occurrence is not entirely associated with VEGF levels in CFXIIID patients and some other related underlying factors, besides FXIII deficiency, may contribute to ICH occurrence in such patients.

Keywords • Factor XIII deficiency • ICH • VEGF

Incidence of Anemia and Thrombocytopenia among Obstetric Patients in Vali-Asre Teaching Hospital, Birjand, South Khorasan

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Abstract

Background: The purpose of this study was to determine the incidence of iron deficiency anemia in an obstetric ward with a secondary objective of determining the platelet count and thrombocytopenia.

Methods: This was a descriptive study of obstetric patients in Vali-Asre Teaching Hospital, Birjand. Data were collected on women who delivered in the hospital during a 3-month period (2017). Data were collected through chart reviews linked with the hospital's database.

Results: Inclusion criteria were met by 200 patients. Anemia in accordance with the World Health Organization's criteria (hemoglobin <11 g/dL and hematocrit <33%) was present in 16/200 (8%) at delivery. Gestational thrombocytopenia was seen in 9.5% (19/200) cases. Mean platelet count at delivery remained at 212×10^3 per microliter.

Conclusion: Although good health care during pregnancy is now provided, anemia continues to affect obstetrical patients and its prevalence in our patient population was relatively high. Further investigation is warranted to better understand the apparent ineffectiveness of iron supplementation. Thrombocytopenia also should be monitored in pregnant women.

Keywords • Anemia • Pregnancy • Prevalence • Obstetric • Thrombocytopenia

Effectiveness of Positive Psychological Intervention on Well-Being and Satisfaction in Mothers of Children with Cancer

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Abstract

Having a child with cancer exerts a negative impact on the mental quality of life of parents, especially mothers, who have a more caring role, and reduces life satisfaction and psychological well-being. Therefore, this study aimed to improve life satisfaction and psychological well-being in the lives of such parents with the aid of the procedures conducted in positive psychological intervention. In this study, 50 mothers of children with cancer who were referred to Imam Reza Treatment Center, in Shiraz, were selected accessibly and then assigned to 2 experimental and control groups randomly. The participants completed SWLS (Satisfaction With Life Scale) and PWBS (Psychological Well-Being Scale). Data were analyzed using the analysis of covariance and SPSS. The findings suggested that positive psychological intervention exerted a positive impact on life satisfaction and psychological well-being.

Keywords • Life satisfaction • Mothers of children with cancer • Positive psychological intervention • Psychological well-being

Etiological Study in Arterial and Venous Thrombosis in Children

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Abstract

Background: Thrombophilia is a medical term used to describe the condition when the blood has an increased tendency to clot. There are many reasons for the blood to have such increased tendency. Thrombophilia in neonate and children is a less recognized disorder despite causing serious problems. Many of the patients who refer with thrombosis in early ages are neglected and not diagnosed with the disease until showing complications in older ages. Our information about thrombophilia is limited and most of the studies are on adult patients. In children, the etiology of thrombophilia is usually categorized into two types, namely acquired and inherited. Such studies are rarely assessed in Iran and never in the city of Arak. In addition, there is a possibility of negligence in the symptoms of arterial and venous thrombosis. Consequently, the present study aimed to assess the etiology of arterial and venous thrombosis in children and to promote the diagnosis and treatment of such patients.

Methods: In a descriptive study, based on hospital files and inclusion/exclusion criteria, all documented diagnoses of patients that have been admitted during 2011-2016 to the pediatric clinic of Amir Kabir Hospital (Arak, Iran) with signs of arterial and venous thrombosis were reviewed. Patients' data, such as risk factors, familial history, thrombosis site (arterial and venous), laboratory data (CBC, Hb electrophoresis, sickle prep, factor V Liden, Pr C deficiency, Pr S deficiency, antithrombin III deficiency, MTHFR mutation, prothrombin G20210A mutation, serum level of homocysteine, serum level of factor VIII), imaging (chest X-ray, CT scan, MRI), and echocardiography were collected and analyzed using the SPSS statistical software (version 20.0)

Results: This study was performed on 17 children with the minimum age of 15 days and the maximum age of 15 years (11 boys and 6 girls). Ten cases had arterial thrombosis (6 boys and 4 girls) and 7 cases had venous thrombosis (5 boys and 2 girls). Based on the chi-square test ($P=0.627$), there was no significant the site of thrombosis with sex and age. Among the 17 cases, 5 cases had MTHFR mutation, 2 cases had elevated serum level of homocysteine, 2 cases had protein C deficiency, and the rest had septic thrombosis, sickle cell anemia, Tetralogy of Fallot, leukemia, lymphoma, Cyanotic heart disease, intermedia thalassemia, Ewing sarcoma, and idiopathic. Furthermore, there was no significant relationship between the site and cause of thrombosis. The most common cause was MTHFR mutation, although factor V Leiden is considered as the most common cause of thrombosis.

Conclusion: Arterial thrombosis is more common than venous thrombosis and the most common etiology is MTHFR mutation.

Keywords • Children • Etiology • Thrombosis

Astatine Can Lead to Acute Hemolysis: A Case Report

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Abstract

Background: Some medications may result in hemolysis with different mechanisms (direct destruction or antibody associated) and lead to anemia. Recognition of such medications may affect the treatment. Herein, an acute hemolytic anemia with astatine is reported.

Case Presentation: A 43-year-old female was referred with the complaint of urine discoloration, dizziness, and weakness. She had a history of using lovastatin because of hypercholesterolemia (LDL: 255) for a short time. She did not have any family history of hematologic disease. She had one episode of hemolytic anemia with atorvastatin three years ago, after which she recovered with its discontinuation.

Laboratory findings were Hb: 10, bill: 2.5 with direct: 0.4, LDH: 560 UA, Blood 2+ and RBC: 1-2, PBS: polychromatic RBC, that showed acute hemolysis. Direct and indirect Coombs tests were negative. Hemolysis evidence was completely relieved after lovastatin had been stopped. G6PD was sufficient after recovery of hemolysis. Other groups of anti-hypercholesterolemia medications were recommended but refused by the patient. She arbitrarily took rosuvastatin (another medication of astatine group) and to our surprise, hemolysis did not occur. She did not have any experience of hemolysis, although we increased the dosage to reach the LDL goal.

Astatine is prescribed for hypercholesterolemia treatment and is well tolerated. Rarely their adverse effects occur that include elevated liver enzymes, rhabdomyolysis, and seldom leads to its discontinuation. Here we report a rare adverse effect of astatine, hemolytic anemia, which was stopped after switching to rosuvastatin.

According to the literature, atorvastatin can help the prevention of hemolysis in some settings (e.g. MS) by stabilizing cell membranes. In this case, we experienced an episode of Coomb's negative hemolytic anemia with astatine. Rosuvastatin did not lead to hemolysis because of differences in structure.

Conclusion: Coomb's negative hemolytic anemia may be a rare side effect of atorvastatin and simvastatin. Rosuvastatin is recommended in patients with hemolysis following astatine.

Keywords • Atorvastatin • Lovastatin • Rosuvastatin

Genetic Study of Afibrinogenemia in Iran

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Abstract

Background: Afibrinogenemia is a rare autosomal recessive disorder caused by fibrinogen deficiency, which is a crucial protein in coagulation. It results from mutations in FGA, FGB, and FGG genes. Each of these genes produces one of the fibrinogen subunits. The present study aimed to investigate different kinds of mutations in genes responsible for afibrinogenemia in Iran.

Methods: Since 2011, six patients from three unrelated families have been referred to Dr. Zeinali's Medical Genetics Laboratory (Tehran, Iran). After obtaining the informed consent, DNA extraction was performed using the salting-out procedure. Genetic testing of these genes was performed using Sanger sequencing.

Results: Three different mutations were identified in two genes. A nonsense mutation and a small deletion were found in the FGA gene. A nonsense mutation was also identified in the FGB gene.

Conclusion: Identification of a causative mutation in afibrinogenemia is valuable as it permits (i) early testing of other at-risk individuals, (ii) to perform carrier detection and prenatal diagnosis, (iii) to understand the genotype-phenotype correlation, and (iv) to assist in therapeutic choices. Furthermore, it is beneficial, as a necessary requirement, to develop new specific treatments, such as gene therapy.

Keywords • Afibrinogenemia • FGA • FGB • Iran

Correlation of Cancer with the Type and Site of Thrombosis

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Abstract

Background: Cancer is a frequent finding in patients with thrombosis with significant morbidity and mortality. Venous thromboembolism in cancer is also associated with a high recurrence rate and worsened quality of life.

Methods: A total of 104 patients, with known underlying cancer, were evaluated according to pathologic report and the new onset of arterial or venous thrombosis. Thrombosis was confirmed by color Doppler ultrasonography and D-dimer test. Diagnosis of pulmonary thromboembolism was made by spiral CT scan of the chest. The direct and indirect risk factors, including catheter-related thrombosis, post operation, association with chemotherapy or metastasis, direct local pressure by the tumor, and the stage of tumor were evaluated. Other direct risk factors such as obesity, age, smoking, and immobilization were also evaluated.

Results: The median age of the patients, aged 17-78 years, was 53.64 ± 13.76 . The most common pathology was firstly adenocarcinoma followed by hematologic malignancy. The most common cancer was colon cancer, hematologic malignancy, pancreas, breast, gastric cancer, and lung cancer, respectively. The patients with advanced stage of the disease had more thrombosis (stage 4 (43.3%), stage 3 (35.6%), stage 2 (15.4%), and stage 1 (1.9%)). About 12.5% of patients had post-op thrombosis before the initiation of chemotherapy and 5.8% were catheter related. The most common site of thrombosis was the lower extremities (56.7%), portal or mesenteric vein (13.5%), and jugular vein (8.7%).

Conclusion: Adenocarcinoma is the most common pathology in patients with cancer and thrombosis. Advanced stage of tumor predisposes patients to thrombosis. The colon, pancreas, and breast cancers are the commonest cancers with thrombosis.

Keywords • Cancer • Thrombosis • Pulmonary thromboembolism

Mean Platelet Volume and Coronary Artery Disease: A Recipe for Cardiologists

Mahdi Shahriari

Abstract

Background: Platelets with high hemostatic activity play an important role in the pathophysiology of coronary artery disease (CAD). The mean platelet volume (MPV) is an indicator of platelet reactivity. Hence, MPV may emerge as a potential marker of CAD risk. Central to the pathogenesis of the occlusive arterial disease is the activation of platelets at sites of vascular injury. The present study aimed to conduct a systematic review comparing the mean difference in MPV between patients with CAD and controls and pooling the odds ratio of CAD in those with high versus low MPV.

Methods: Forty-two studies were included in this systematic review.

Results: The MPV was significantly larger in patients with CAD than controls, with the mean difference of 0.70 fL (95% CI: 0.55-0.85). The mean difference of MPV in patients with acute coronary event and in patients with chronic stable angina was 0.84 fL (95% CI: 0.63-1.04) and 0.46 fL (95% CI: 0.11-0.81), respectively. Patients with larger MPV (≥ 7.3 fL) also had greater odds of having CAD than patients with smaller MPV with a pooled odds ratio of 2.28 (95% CI: 1.46-3.58). In studies (n=3) that evaluated the assessment of restenosis after angioplasty, a positive correlation between MPV > 8 fL and change in minimal luminal diameter between post angioplasty and follow-up angiography were observed ($r=+0.56$, $P=0.016$).

Conclusion: Larger MPV was associated with CAD. Hence, it might be helpful in risk stratification. Platelet size may influence the development of restenosis after successful coronary angioplasty, thus patients with high pre-procedural MPV values might benefit from an intensified antiplatelet therapy after coronary interventions.

Keywords • Angiography • Blood platelets • Coronary artery disease

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Thrombophilia in Children: How to Investigate and Manage

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Abstract

The human coagulation and fibrinolytic systems are dynamic and age dependent. Although in the neonatal period, hemostasis is physiologically immature, but it may contribute to morbidity in the sick and preterm infant with and without sepsis. The hemostatic system matures during the early infancy with most hemostatic parameters reaching adult values by 6 months of age even in premature infants. In addition, there is evidence of an accelerated maturation pattern in premature infants showing similar levels of coagulation proteins to term infants by 6 months of age.

In the field of pediatrics, venous thromboembolism (VTE) is increasingly recognized and is a subject for pediatric hematologist consultation. In children, clinical trials in this area are largely extrapolated from adult practice. This approach is unsatisfactory for a few reasons. Firstly, potential differences in the mechanisms for VTE in this age group should be considered. Secondly, age dependency in many aspects of hemostasis, especially in the neonatal period, has a significant impact on the use of anticoagulants in pediatrics. Thirdly, children may survive for a prolonged period following these events such that long-term consequences should be considered in this age group. The present guideline is aimed is to provide a rational basis for the investigation and management of children (from one month to 16 years with VTE). This guideline is targeted at pediatric hematologists and pediatric residents who are involved in the management of children and adolescents with VTE.

Keywords • Child • Blood coagulation • Hemostasis • Anticoagulation • Embolism

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There is A Strong Relation between HLA Alleles and the Risk of Inhibitor Formation in Hemophilia Patients

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Abstract

Background: Hemophilias, including hemophilia A and B, are the most common inherited bleeding disorders. It is estimated that the prevalence of hemophilia A and B are 105 and 28 per million males respectively. Neutralizing antibodies constitute a major obstacle in the treatment of hemophilia patients. Recently, some studies have shown an association between HLA class II and inhibitor formation.

Methods: In this review article, we surveyed the available literature in PubMed during 2000 to 2015 to find original articles, bibliographic reviews, and books.

Results: In a study carried out in Germany, a positive association between HLA alleles and inhibitor formation was seen in the DRB1*15:01 and DQB1*06:02. Similarly in Thai people, there was also an association between DRB1*15 and inhibitor formation. Another study in the United Kingdom showed a correlation between DQA1*01:02 and inhibitor formation. However, Japanese people showed an extremely different association: DR4.1 (DRB1*04:01), DQB1*04, and DQA1*03:01 were correlated with inhibitor formation. Moreover, it was demonstrated that some HLA alleles were able to play a protective role against inhibitor formation; these included HLA-C*05, HLA-A*24, HLA DQB1*05:02, and HLA DRB1*16.

Conclusion: Our study showed a significant association between HLA alleles and the risk of inhibitor formation in hemophilia patients. Our results also indicated that the alleles were different in various ethnicities. A similar study among Iranian people can provide useful information for predicting the risk of inhibitor formation.

Keywords • HLA typing • Hemophilia • Inhibitor formation • HLA-DRB1 • HLA-DQB1 • Human leukocyte antigen-A • Human leukocyte antigen-B

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Genetic Diagnosis of Factor X Deficiency in Iran

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Abstract

Background: Factor X deficiency is a rare autosomal recessive disorder caused by mutations in the F10 gene. The F10 gene (13q34) contains 8 exons and encodes coagulation factor X, which is a serine protease and has an important role in the common pathway of thrombus formation. The present study aimed to report the results of genetic diagnosis of factor X deficiency in five patients in Iran.

Methods: A total of 5 patients, affected with factor X deficiency who referred to Dr. Zeinali Medical Genetics Laboratory (Tehran, Iran), were selected for the present study. DNA extraction was performed using the salting-out method. Sanger sequencing was used to screen all of the 8 exons and their boundaries of the F10 gene. In silico studies were carried out using SIFT, PolyPhen, and Mutation Taster.

Results: Three missense and two small deletions were identified in the studied cases among which 3 were novel mutations. Segregation study and in silico analysis showed that the novel mutations can be pathogenic.

Conclusion: High prevalence of consanguineous marriages in Iran can increase the incidence of different rare autosomal recessive disorders. More studies are required to identify the frequency of different mutations in the F10 gene in Iran. The results of these studies might be helpful in identifying the genetic causes of factor X deficiency and prenatal diagnosis in this country.

Keywords • Factor X deficiency • F10 gene • Mutation

Assessment of RBC Storage Lesions during Red Cell Storage

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Abstract

Background: Red blood cells (RBCs) undergo biochemical and morphological alterations during storage, which are known as red cell storage lesions causing decreased RBC quality. Microvesicles (MVs) as one of them may be derived from various blood cells and have key roles in several biological processes. The aim of the present study was to evaluate various storage quality measures in RBC concentrates during cold storage under blood bank condition.

Methods: Twenty leuko-depleted packed RBCs bags from healthy donors were prepared and stored at 4 °C for up to 42 days. Samples were withdrawn at 7 different times and evaluated for various hematological, biochemical, and hemolysis measures. Also, red blood cell microvesicles (RBC-MVs) were separated and characterized based on the expression of glycophorin A (Gly.A) antigen.

Results: The assessment of RBCs during cold storage showed a significant increase in the hemolysis rate, hematocrit, total hemoglobin, plasma potassium, and plasma lactate ($P<0.0001$), while significant decreases in plasma sodium and glucose ($P<0.0001$) were observed. A significant increase was also identified in the RBC osmotic fragility ($P<0.001$). During the storage of RBCs in SAGM, the MVs count increased significantly. The majority of the MVs (87.3%) had positive staining for Gly.A, and it correlated with the changes in the hemolysis rate ($r=0.77$; $P<0.001$)

Conclusion: Storage of RBCs is associated with important changes that influence biochemical parameters, hemolysis, and microvesiculation process, which generally affects the product quality and may contribute to a negative post-transfusion outcome.

Keywords • Blood bank • Glycophorin • Red blood cell • Storage lesion

An Overview Analysis of Blood Donation on Religious Days: An Experience in Iran

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Abstract

Background: Religious beliefs are one of the positive motivations for blood donation. We aimed to compare blood donation on religious days and normal days with respect to the donor pattern and the safety of donors.

Method: In a cross-sectional study, the donors' characteristics and the blood safety of the blood donors on religious days (2009–2013) were compared with blood donors who referred 1 month before religious days.

Result: Most of the donors on the religious days were male and 1st-time blood donors ($P < 0.001$). The prevalence rates of hepatitis B and hepatitis C were lower in the blood donors on religious days ($P < 0.001$).

Conclusion: Although highlighting religious beliefs is an important motivating factor for blood donation, providing facilities for blood donation on special religious days is one of the significant ways to encourage people to start and continue blood donation. Moreover, long-term participation of individuals as active donors is related to the blood donation experience, awareness of the continuous need for blood in the community, and the importance of regular blood donation.

Keywords • Blood donation • Motivation • Blood donor • Blood safety

Blood Donors' Return Rate

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Abstract

Background: Understanding current blood donor patterns with regard to their demographic characteristics and return rates will be beneficial when implementing measures to promote blood donation, encourage new blood donor recruits, and help retain existing donors. This study aimed to determine current blood donor rates and related factors.

Methods: This cohort study was conducted on 1,800 blood donors, who donated blood at Shiraz Blood Transfusion Center, Iran from 26th November 2009 to 26th December 2009. Blood donors' return rate and its related factors were investigated in a 5-year follow-up.

Results: The overall return rates of the blood donors indicated a significant decline (50.2%, 44.1%, 36.2%, 36.4%, and 25.7%) over the 5-year follow-up. The return rates for 1st-time donors were 28%, 23.2%, 19.8%, and 10.1% over the study period. These results indicated a pattern of decline in the return rates of the blood donors ($P < 0.05$). In addition, we found that the return rates were higher among males, older donors, low educated donors, Rh-negative donors, regular donors, and donors with a history of frequent blood donations.

Conclusion: The low return rate of blood donors shows the need for designing and evaluating strategies to retain blood donors. Marketing actions and the provision of promotional materials aimed at increasing return rates should be reinforced, particularly with respect to youngsters, females, and 1st-time donors.

Keywords • Blood donors • Blood donation • Return rate • Blood supply • Donor retention • Blood donor recruitment

Elevated Levels of RBC-Derived Procoagulant Microvesicles in Stored RBCs

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Abstract

Background: During storage, red blood cells (RBCs) undergo structural and biochemical alterations, which are collectively called RBC storage lesions. These lesions cause a decrease in RBC recovery and survival. In addition, erythrocytes release an increasing number of microvesicles (MVs) throughout cold storage that have key roles in biological processes. We aimed to investigate the procoagulant activity of RBC-derived MVs during storage.

Methods: Twenty packed RBCs were stored up to 42 days. Samples were taken at 7 different times and evaluated for the presence of RBC-MVs. Microvesicles were separated and following the filtration, flow cytometry was used to characterize the RBC-MVs based on the expression of glycoprotein A (Gly.A) and annexin V (AnnV) antigens. The coagulant activity of the RBC-MVs was tested by clotting time (CT) and procoagulant activity (PCA) assays. The results were compared before and after filtration.

Results: Flow cytometry revealed a 17.6-fold increase in the RBC-MVs after 6 weeks of storage. Significant correlations were found between AnnV+ MVs and PCA ($r=0.96$; $P<0.001$) and CT ($r=-0.77$; <0.001), associated with increased PCA and shortened CT with RBC aging. Filtration of the samples efficiently removed the MVs ($P<0.001$) and also reduced the in vitro PCA of the MVs ($P<0.001$).

Conclusion: RBC-MVs are procoagulant agents (particularly AnnV-positive MVs) that may contribute to post-transfusion complications. It has been suggested that the filtration of supernatants from red cell concentrates may reduce the risk of transfusion-induced blood coagulation. Given their probable role in hemostatic response, MVs might serve as an independent index for predicting the quality of RBC products.

Keywords • Filtration • Microvesicles • Procoagulant activity
• Red blood cell • Storage

Relationship between the Duffy Blood Group and the Incidence and Severity of Preeclampsia in Pregnant Women Referred to Hospitals Affiliated to Shiraz University of Medical Sciences

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Abstract

Background: Preeclampsia is a disease with an unknown cause in pregnant women. Understanding and managing the risk factors of preeclampsia can reduce mortality and morbidity in the affected patients. The aim of this study was to evaluate the relationship between the Duffy blood group and the incidence and severity of preeclampsia in pregnant women referred to hospital affiliated with Shiraz University of Medical Sciences.

Methods: In a cross-sectional study, we compared patients with mild and severe preeclampsia with a control group in terms of the Duffy blood group. The data were analyzed using SPSS, version 16.

Results: Out of a total of 119 participants enrolled, 66 (55.5%) were counted as the control group, 36 (30.3%) as mild preeclampsia, and 17 (14.3%) as severe preeclampsia. The mean age of the participants was 29.49 ± 5.26 years. There was no significant difference between the groups with respect to age ($P=0.56$). In this study, there were no statistically significant differences between the groups in terms of FY*A ($P=0.34$) and FY*B ($P=0.92$) Duffy antigens.

Conclusion: We found no relationship between the Duffy blood group and the incidence and severity of preeclampsia in the pregnant women.

Keywords • Duffy • Blood group antigen • Preeclampsia • Pregnancy

Peripheral Blood Stem Cell Apheresis in Small Children is Difficult!

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Abstract

Background: In low-weight children with cancer and healthy donor children, peripheral blood progenitor cells (PBPCs) have largely replaced the bone marrow as the source of autologous and allogeneic stem cells in part because of their relatively easy collection. However, there is a concern regarding medical, psychosocial, and technical difficulties in small children.

Methods: We retrospectively analyzed peripheral blood stem cell apheresis in 40 collections. Thirty-one patients were with cancer (18 patients with neuroblastoma, 4 patients with retinoblastoma, 5 patients with germ cell tumor, 1 patient with hepatoblastoma, and 3 patients with Wilms' tumor) and 9 healthy children donors. The study was conducted between 2012 and 2016. Peripheral stem cell apheresis was performed in the MAHAK Cancer Children's Hospital in a nice room for children where the patients stayed with their families. Patients were not routinely sedated. PBPCs were collected using a COBE Spectra cell separator (COBE, Denver, CO, USA). Harvesting was performed after 5 days' mobilization.

Results: Mean body weight was 10.6 kg (range=7.5 kg–15 kg) for a median age of 3 years (range=9 mon–4.5 y). Mean duration of harvesting was 205 minutes (range=164–270 min). Mean volume of stem cell collection was 135 mL (range=110 mL–240 mL). The mean number of total nucleated cells collected was 5.4×10^8 /kg (range= 3.2 – 9.9×10^8 /kg recipients). No side effects occurred. The children did not require an additional hematopoietic progenitor mobilization or additional apheresis on other days. PBSC collection was without transfusion in the healthy donor children.

Conclusion: PBSC collection may be difficult in small children owing to the large-volume apheresis.

Keywords • Children • Apheresis • Stem cell

Positive Effect of Educational-Clinical packages on the Skill of Nursing Students; from Phlebotomy to Transfusion and Hemovigilance

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Abstract

Background: Blood transfusion is a life-saving treatment if performed correctly. However, evidence suggests that blood and its derivatives are often used inappropriately. While nurses are the only operators of blood transfusion in hospitals, their knowledge of blood and its products, usage, care, and reporting is limited. It seems that they have inadequate knowledge about hemovigilance. Consequently, the present study aimed to determine the effect of educational-clinical training package on the skill of nursing students; from phlebotomy to transfusion and hemovigilance.

Methods: The study was performed on all students in the sixth semester of the nursing undergraduate program (n=26), who were undergoing medical training and surgical nursing in blood diseases. The students in the intervention group were trained over a period of 4 weeks and in 4 steps; whereas routine courses were held in the control group. Then, the skill of both groups was evaluated using a checklist. The data were analyzed using the SPSS statistical software.

Results: The results showed a significant increase of scores in blood transfusion, disease control, and hemovigilance in the intervention group (87.34±3.48) compared to the control group (38.15±5.26). The results indicated that the new training method was more effective than the traditional method.

Conclusion: Considering the role of patient-centered care in nursing and the fact that nurses are the only operators of blood transfusion in hospitals, the proposed method of teaching is recommended.

Keywords • Blood • Phlebotomy • Transfusion • Hemovigilance
• Proficiency • Nursing students

Prevalence of Acute Blood Transfusion Reactions in Hospitalized Patients

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Abstract

Background: The most important goal of blood transfusion centers in the world is to reduce complications, improve blood transfusion safety, and patient health. This study aimed to investigate the prevalence of acute complications of blood transfusion.

Methods: A total of 6,130 patients that received blood during 2016-2017 were evaluated for acute blood transfusion reactions. The patients were admitted to various wards (emergency, CCU, post CCU, NICU, Cooley's anemia, hemodialysis, surgical, and operating rooms) at Motahari Hospital affiliated with Jahrom University of Medical Sciences (Jahrom, Iran). The data were analyzed by the chi-square test using the SPSS software.

Results: Of the 6,130 patients, 40 (3%) patients experienced acute complications of blood transfusion and 6,110 (97%) patients reported no side effects. Of the 40 patients with complication, 23 (57.5%) patients showed febrile *non-hemolytic* transfusion reaction, 16 (40%) patients had an allergic reaction, and 1 (2.5%) patient had transfusion-associated circulatory overload (TACO).

Conclusion: The prevalence of blood transfusion reactions in this blood transfusion center was within the normal range (i.e. 3% at Motahari Hospital vs. 0.5-6% international norm). Considering its importance and risk to patients, improvements are required to reduce the incidence of complications.

Keywords • Blood transfusion • Prevalence • Transfusions reaction

Evaluation of Changes in Blood and Blood Products Transfusion Indices: A Case Review

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Abstract

Background: Increasing demand for blood and blood products can impose additional costs to blood transfusion centers, increase complications due to blood transfusion, depletion of blood bank reserves, lack of proper blood and blood product distribution to various centers, and poorer quality of blood units. The present study aimed to evaluate changes in blood and blood product transfusion indices after a 3-year activity of the blood bank committee of Mofid Children Hospital (Tehran, Iran).

Methods: All request forms for blood and blood products from the year 2011 were reviewed based on the type of products and wards at Mofid Children Hospital. Then, blood bank indices were calculated. Following a 3-year activity of the blood bank committee, the corresponding data were reviewed and compared.

Results: During 2011, a total of 13,653 units of blood and blood products were requested in all hospital wards in which 10,472 units (77%) were transfused, 3,181 units (23%) canceled, and the C/T ratio was equal to 1.43. Following a 3-year activity of the blood bank committee, 17,946 units of blood and blood products cross-matched in which 14,775 units (83%) transfused, 3,171 units (17%) canceled, and the C/T ratio was equal to 1.33 ($P < 0.0001$). The activity of the blood bank committee at surgical wards optimized the C/T ratio from 2.83 to 2.13.

Conclusion: It is shown that the activity of the blood bank committee during the past 3 years optimized the use of blood and blood products at Mofid Children Hospital, more particularly in surgical wards.

Keywords • Blood transfusions • Blood banking • Cross matching • Blood

Essential Role of Inventory Blood Management in Reducing Waste in Blood Transfusion Services

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Abstract

Background: Blood inventory management has an important role in blood transfusion services. It can help to obtain the maximum quantity and quality of safe blood. A maximum quantity of blood components leads to a better management of a disaster. The present study aimed to investigate the rate of blood component discard and the impact of corrective actions in maintaining proper blood supply in blood bank centers of Ilam (Iran).

Methods: A cross-sectional study was conducted to collect data from Ilam blood transfusion centers. The data included information such as the number and status of wastage blood components, as well as corrective actions. The data were analyzed by the t test method using the SPSS statistical software (version 2-0.0).

Results: During 2014, platelet concentrates recorded the highest discard rate (34.7%) followed by fresh frozen plasma (20.5%). The rate of discarded packed red blood cells (RBCs) was 10.5%. The total discard of blood products in 2014 and 2015 was 36.5% and 14%, respectively. The total number of wasted fresh frozen plasma recorded at 15.2% (lower than the previous year) and the waste of platelet concentrate was at 20.1%. Overall, the total wastage of blood components for the year 2014 and 2015 showed a reduction in 2015 ($P=0.001$).

Conclusion: Blood transfusion centers in Ilam have increased provision for hemovigilance unit, management of blood donation, and taking corrective actions. As a result, a reduction in total wastage blood product has been achieved.

Keywords • Blood supply • Blood component • Hemovigilance

Demographic Factors of First-Time Donors in Ahvaz

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Abstract

Background: Annually, approximately 1.5 million donors donate their blood in Iran of which 25% are first time donors. It is reported that two-thirds of the total hepatitis B, hepatitis C, and HIV cases are positive. The transition from a first-time donor to regular voluntary blood donor reduces the risk of transfusion-transmissible infections (TTI) and leads to higher blood safety. The present study aimed to analyze demographic factors among first-time blood donors in Ahvaz.

Methods: A cross-sectional study was conducted at the blood transfusion center in Ahvaz (Iran) during 2013 to 2016. Demographic factors were age, gender, and the education of donors.

Results: The results indicate a decrease in the percentage of first-time donors from 18.1% (in 2013) to 17.2% (in 2016). For the female donors, the rate reduced from 6.3% (in 2013) to 5.8% (in 2016). The average age of donors also declined and the majority aged between 31-35 years. The educational level of about 70% of the first-time donors was diploma or less.

Conclusion: A reduction in the age of blood donors is a positive news. However, it is more important to lower it to the minimum permissible age and recruit young first-time donors, particularly students due to their perception of TTI. Furthermore, counseling and issuing donor cards may also increase the likelihood of turning first-time donors into regular blood donors. The percentage of female donors, as a source of healthy blood donors, compared with the mean women donors in the country (4.4%) is good but not satisfactory.

Keywords • First-time donors • Demographic parameters • Donor Recruitment

Demand and Consumption Pattern of Packed Red Blood Cell Units in Open Heart Surgery

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Abstract

Background: Cardiovascular diseases are one of the main causes of death worldwide. In advanced cases of such diseases, some of the patients may undergo open heart surgery. Due to the high risk of bleeding during the surgery, preparing fresh red cell units is critical. On the other hand, due to the increasing demand from other units and the shortage of some blood types, a relative estimation of demanded blood bags during a surgery will prevent unnecessary blood reservation. The present study aimed to address this issue and to investigate the demand and consumption pattern of red blood cell products in open-heart surgery.

Methods: A cross-sectional study based on descriptive method was performed on all heart patients who underwent open heart surgery. The data related to age, gender, the number of cross-matched, as well as consumed and unused packed red blood cell bags was recorded. The data were analyzed using the SPSS software and discretional statistics (e.g. frequency, mean, and standard deviation), as well as inferential statistics (e.g. Pearson correlation coefficient test, Eta, Phi and Cramer's) were determined.

Results: The population of the study consisted of 203 patients with different genders, but equal in age (60 years old). The average number of cross-matched, consumed, and canceled blood bags in female patients was 3.67, 1.03, and 2.3793, respectively; while in male patients, it was 3.5354, 2.517, and 1.5, respectively. There was no significant correlation between the variable of gender and the number of consumed and canceled blood bags (P value of 0.18 and 0.07, respectively).

Conclusion: There was no significant correlation between the variables gender and age with the number of consumed and unused blood bags.

Keywords • Open heart surgery • Cross-katch • Packed red cells

Frequency of Hepatitis B and C among Jiroft Blood Donors based on Demographic Characteristics

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Abstract

Background: Viral hepatitis is considered as the most important health problem in many human societies. Investigating the frequency of hepatitis B and C virus infections in a population of blood donors not only helps to assess the regional health of blood donors, but it also provides valuable data regarding the epidemiology of these infections. The present study aimed to determine the prevalence of hepatitis B and C among Jiroft blood donors based on demographic characteristics during 2011-2016.

Methods: In the present cross-sectional study, the required information, including demographic characteristics and blood test results of all blood donors during 2011 to 2015 was extracted from the records. Data were analyzed using descriptive statistics (frequency and percentage) using the SPSS statistical software (version 22.0).

Results: The total number of blood donors was 36,117 people. The frequencies of hepatitis B and C were 3 and 4 per 10,000, respectively. The highest infection rates were in the 21-30 year age group. The prevalence of hepatitis B and C were higher among married, male, and first-time donors.

Conclusion: The prevalence of hepatitis B and C infections in blood donors has not increased during the years 2011-2016 and has almost declined. This indicates the effectiveness of screening methods and/or lower prevalence of viral infections among Jiroft blood donors. Consequently, due to a low prevalence of viruses transmitted through blood in regular blood donors, the continuance of using blood provided by the regular donors must be considered as the priority source of safe blood supply.

Keywords • Hepatitis B • Hepatitis C • Blood transfusion • Blood donors

The Prevalence of Toxoplasmosis in Iranian Blood Donors: A Systematic Review

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Abstract

Background: Toxoplasmosis is caused by *Toxoplasma gondii* and is a parasitic, infectious, and prevalent disease in the world. In the acute phase of infection, the parasite is in all body fluids. Due to *Toxoplasma* resistance to temperature controlled blood bank refrigerators and lack of diagnostic tests for the parasites before transfusion, the recipient of the blood could also be infected if a healthy donor is infected with the parasite. The present study aimed to evaluate the prevalence of IgM and IgG antibodies against *Toxoplasma gondii* infection in Iranian blood donors.

Methods: In this systematic review, Persian language (SID) and English language (PubMed, Scopus, ScienceDirect, and Google Scholar) databases were searched without any time limitation. The search included keywords such as Toxoplasmosis, blood donors, blood transfusion, prevalence, and Iran. Eventually, 11 articles fulfilled the inclusion criteria and selected for the review.

Results: The result of the reviewed studies indicated that the incidence of antibody IgG was 31% (95% confidence interval (CI): 21%-41%) and IgM was 1% (95% confidence interval (CI): 0%-2%). The highest and lowest IgG percentage was related to Hamadan and Fars, respectively. The highest and lowest value of IgM was related to Fars and Zahedan, respectively.

Conclusion: Due to the lack of *Toxoplasma* screening test in blood transfusion, its inclusion in the test chart of the blood transfusion institutions is recommended. Transmission of the parasite would cause toxoplasmosis and worsen the symptoms of a patient with weak immune system.

Keywords • Toxoplasmosis • Blood donors • Blood transfusion • Prevalence • Iran

The Evaluation of CCR5 Co-Receptor Transfer through Platelet-Derived Microparticle and its Role in Viral Distribution

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Abstract

Background: In addition to the main receptor for the HIV virus entrance, co-receptor is necessary. Past studies have proven the evidence of transferring surface receptors through microvesicles. Platelet microparticles (PMP) have the ability to transfer materials such as arachidonic acid. The present study attempted to check the role of PMP as a transporter of CCR5 co-receptor between two cells.

Methods: K562 cell lines and Nalm6 were seeded in medium RPMI1640 and 10% FBS. PMP was separated from platelet concentrate bags on the third-day expiration by 3-step centrifugation. Then, the concentration by Bradford method was determined. About 100,000 cells with different concentrations of PMP (125, 250, and 500 mg/ml) were co-incubated for an hour at 5% CO₂ incubator 37°C. To confirm the transfer of CCR5, K562, and U937, Daudi cell lines were separately incubated for an hour at 5% CO₂ incubator 37°C with different concentrations (10-250 mg/ml) of PMP. Then, cells were evaluated for CCR5, CXCR4, and PMP for CCR5 and analyzed by Partec flow cytometry and FloMax software.

Results: The transfer of CCR5 by PMP in 125, 250, and 500 mg/ml from K562 to Nalm6 was not confirmed for two cell lines in co-culture. On the other hand, the transfer of surface receptor CXCR4 by PMP to cell line was confirmed in different concentrations. This transfer was increased with the increasing concentration of PMP.

Conclusion: The transfer of CXCR4 in various concentrations was checked and confirmed. However, the result was not confirmed for CCR5 transfer by PMP in three concentrations. Further research in this area is recommended.

Keywords • CCR5 co-receptor • CXCR4 co-receptor • Platelet derived microparticle • HIV virus

Herpes Zoster in Cancer Patients

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Abstract

Background: Herpes zoster is a painful reactivation of latent varicella-zoster virus infection. Herpes zoster risk increases with age and it can occur both in apparently immunocompetent and immunocompromised hosts.

Methods: Patients with known underlying cancer and localized or disseminated herpes zoster were evaluated. Diagnostic criteria based on the signs and symptoms of herpes zoster are usually distinctive enough to make an accurate clinical diagnosis, once the rash has appeared. Laboratory testing in cases with less typical clinical presentations and disseminated herpes zoster was done by serologic methods and PCR.

Results: The median age was 52.6 (range 18-82) with 27 males (54%) and 23 (46%) females. The most common cancers with herpes zoster were non-Hodgkin's lymphoma (18%), breast cancer (18%), Hodgkin's lymphoma (14%), chronic lymphocytic leukemia (12%), gastric cancer (10%), multiple myeloma (8%), and prostate cancer (8%). The most common sites of herpes zoster were the trunk (60%) and extremities (18%). The rate for the head and neck was 14%, pelvic 2%, and disseminated zoster infection was seen in 3 cases (6%), including CLL, NHL, and ALL. The median duration of zoster reactivation in patients' post-chemotherapy was 24.51 months (3-60 mo).

Conclusion: The most common predisposing factors for herpes zoster reactivation are aging and immunosuppression. It can occur in the lower age range of cancer patients who receive chemotherapy and post-chemotherapy until 5 years post-chemotherapy. Immunosuppression after chemotherapy or radiotherapy and autologous stem cell transplantation is prolonged. It means patients with cancer have prolonged T-cell dysfunction after treatment.

Keywords • Herpes zoster • Cancer • Immunosuppression

Association between the Cytotoxic T-Lymphocyte Antigen-4 (CTLA-4) Polymorphisms and Torque Teno Virus (TTV) Infection Post Hematopoietic Stem Cell Transplantation

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Abstract

Background: Cytotoxic T-lymphocyte antigen-4 (CTLA-4) is assumed to play the role of a crucial negative regulator of the immune system. Association between co-stimulatory molecule gene polymorphisms and viral infection post hematopoietic stem cell transplantation (HSCT) may be related with clinical outcomes, especially acute graft versus host disease (aGVHD). The objective of the present study was to investigate the association between CTLA-4 gene polymorphisms, including -1722 T/C, -1661 A/G, -318 C/T, and +49 A/G, and the Torque teno virus (TTV) infection post HSCT in patients with and without aGVHD.

Methods: A total of 71 recipients were included in this study. CTLA-4 gene polymorphisms were evaluated by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method.

Results: The results revealed that the GG genotype of the CTLA4 +49 A/G was significantly more frequent in the TTV-infected HSCT patients than that of the non-infected ones. Moreover, the CTLA-4 -1722 CC genotype was significantly higher in the TTV-infected HSCT patients who experienced no aGVHD. The -1661 AA and GA genotypes and -318 TC genotypes were significantly more frequent in the TTV-infected patients who experienced a low grade of aGVHD. Moreover, the +49 GG and -1661 GA genotypes had a significantly higher frequency in the TTV-infected patients who experienced grade 1 and grade 2 aGVHD, respectively, than those of the non-infected ones.

Conclusion: Therefore, CTLA-4 polymorphism may be implicated in the prevalence of the TTV infection following stem cell transplantation. Evaluation of other co-stimulatory molecules should be taken into account.

Keywords • Torque teno virus (TTV) • Single-nucleotide polymorphisms (SNPs) • Cytotoxic T-lymphocyte antigen-4 (CTLA-4)

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Vicious Crosstalk of Inflammation and Cancer: A New Horizon to Hematological Malignancies Dilemma

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Abstract

Sepsis, as a host systemic inflammatory response to infection attack in the bloodstream, is a complex chain of proinflammatory cytokines cascade. If chronicity, it will represent a facilitating role in the chronic immunological condition such as hematological cancer onset or progression. The present study aimed to evaluate new directions on etiologic molecular pathways linking inflammation, hematological malignancies, and immunoserological factors helping to decipher this complicated microenvironment. This paper was conducted to outline studies published in PubMed, Scopus, and ScienceDirect databases, as well as Google Scholar search engine from 2000 up to February 2017 by using five keywords. Then, the articles were screened to identify the above-mentioned goals.

Of the 205 initial articles, 95 articles were eventually selected for the study purpose. Invasive fungal, catheter-related bloodstream and gram-negative bacterial infections are pioneer causes of morbidity and mortality in immunocompromised hematological malignancies affected patients, in particular, acute lymphoblastic leukemia, multiple myeloma, and lymphoma. Rapidly excessive increased concentrations of C-reactive protein as an acute phase protein, IL-6 as an activator of JAK2/STAT3 leading to unchecked cell proliferation and neoplasia, as well as presepsin and procalcitonin, are the most useful immunobiomarkers for early detection of infection and death risk screening.

Growing evidence on death rate in oncohematological diseases forces us to discover interactions and overlaps between cancer and infections, which will be a promising window to overcome concerns about late diagnosis and poor prognosis.

Keywords • Immunobiomarker • Crosstalk • Diagnosis • Infectious diseases • Hematological cancers

The Effect of Methanolic Extract of Aerial Parts of *Artemisia Annua* on Proliferation and Apoptosis of Acute Lymphoblastic Leukemia Cell Lines, Nalm-6, and Reh

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Abstract

Background: Acute lymphoblastic leukemia (ALL) is the most common malignancy among children. Due to the adverse effects of chemotherapy treatment, there is an increasing interest in natural compounds for the treatment of malignancies. *Artemisia annua* is reported to show cytotoxic effects on various cancer cell lines. The present study aimed to investigate the cytotoxic effects of *Artemisia annua* extract on acute lymphoblastic leukemia cell lines.

Methods: Nalm-6 and Reh cells were cultured and treated with various concentrations of *Artemisia annua* extract. Then, cell viability was evaluated using MTT assay for 48 and 72 hours. Caspase-3 activity assay and flow cytometry following annexin V and propidium iodide staining were used to assess apoptosis. Statistical analysis was evaluated by one-way ANOVA test.

Results: *Artemisia annua* extract showed IC₅₀ of 90 µg/ml on Nalm-6 and IC₅₀ of 70 µg/ml on Reh cells after 48 hours. The cytotoxic effect after 72 hours was noticeable (P<0.001). Flow cytometry results showed that *Artemisia annua* extract concentration of 40 µg/ml increases the percentage of apoptotic cells compared with the control groups (P<0.05). Significant increase in Caspase-3 activity was observed after treatment with *Artemisia annua* compared with the control groups (P<0.01).

Conclusion: The results showed that the methanolic extract of aerial parts of *Artemisia annua* exerts cytotoxic and inhibitory effects on Nalm-6 and Reh cells.

Keywords • Acute lymphoblastic leukemia • *Artemisia annua* • Apoptosis • Cytotoxicity

Importance and Applications of Exome Sequencing in Acute Myeloid Leukemia: A Systematic Review

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Abstract

Background: Next-generation sequencing (NGS) is a disruptive technology that has revolutionized the oncology. Exome sequencing is an application of NGS that provides cost-effective sequencing in terms of turnaround time and price. Acute myeloid leukemia (AML), as the 2nd most frequent hematological malignancy, obtains biologically informative alterations that can be interrogated from exome sequencing data. In order to determine the importance and applications of exome sequencing in AML, we systematically reviewed all published articles between years 2000 and 2017.

Methods: A search in PubMed with MeSH heading "Exome" OR "Exome" in the "Title Abstract" AND "Acute Myeloid Leukemia" in the "Title" was performed.

Results: The search yielded 37 articles, 9 of which were review articles and 28 were potentially appropriate for inclusion. In 4 articles, transcriptome analysis and in 7 articles, genomic microarrays were used in addition to exome sequencing. Evaluating the AML course in a serial time point was done in 10 studies. Five studies were specifically on pediatric AML. The most application was on genomic profiling (8; 27%), followed by clonal evolution (5; 17%). Other important aspects were analyzing potential germline mutations in familial AML patients (3), evaluating prognosis (3), genetic risk prediction (1), diagnosis (2), monitoring (1), residual disease (2), and relapse (1).

Conclusion: Exome sequencing has improved our insight into the different aspects of AML, especially in pathogenesis, diagnosis, and prognosis. It has the potency to be used in molecular classification and clinical decision-making.

Keywords • Exome • Acute myeloid leukemia • Systematic review

in Acute Myeloid Leukemia

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Abstract

Background: Acute myeloid leukemia (AML) constitutes less than 1% of all cancers and 25% of all cases of leukemia. It was estimated that among 52,380 new cases of leukemia in the United States in 2014, 18,860 (36%) were AML cases and among 24,090 estimated leukemia deaths, 10,460 (43%) were due to AML. Identification of the clinical features and possible risk factors for early mortality trends in AML is extremely important for the determination of the overall management strategies of the disease course.

Methods: Forty-six new cases of adult *de novo* AML, diagnosed and confirmed in Shahid Ghazi Hospital (Tabriz, Iran), from 2012 to 2014, were included. The ethics committee of the university approved the research. Cases that had received any treatment and with present or past other related diseases were excluded. Patients who died within 1 month of diagnosis were chosen.

Results: Twelve (26%) patients had early deaths in the 1st month of treatment. Results showed that early death was more common in the females and under the age of 60.

Forty-one percent of the patients had blood group B and totally, anemia, leukocytosis, thrombocytopenia, M3 (FAB classification), and high range of LDH (especially in the females) were common.

Conclusion: In recent decades, the mortality rate of leukemia has declined in developed countries. A study in Iran reported that the general mortality rate of leukemia slightly increased between 1995 and 2004, from 0.44 to 2.54. Therefore, future studies on mortality prediction and management would be crucial.

Keywords • Acute myeloid leukemia • Mortality • Iran

Acute Lymphoblastic Leukemia in a 15-Day-Old Neonate

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Abstract

Neonatal acute lymphoblastic leukemia (ALL) is an exceedingly uncommon disease in newborn babies. It is usually diagnosed at birth or within the 1st month of life. The etiological considerations in neonatal ALL include chromosomal defects, intrauterine environmental insults, viral infections, and exposure to radiation during pregnancy. T-cell phenotypes are much less common in infants, while myeloid antigen co-expression and the absence of CD10 expression are more frequent in infants than in older children.

A 15-day-old female neonate, weighing 4 kg, from Lorestan, Iran, was admitted to the Department of Pediatric Neonatology of our hospital. Complete blood count revealed hemoglobin of 10.6 g/dL and total white cell count of 220000/mm³. The differential count yielded neutrophils of 08%, lymphocytes of 24%, and atypical cells of 68%. Platelet count was <20×10⁹/L. Chest X-ray demonstrated patchy infiltrations in both lung fields. Cerebrospinal fluid study was positive for blast cells and central nervous system status 3 (≥5WBC/cmm³ with blasts). Immunophenotype and karyotyping were done, which showed 46XY. Unfortunately, her parents refused chemotherapy. Neonatal ALL in children may mimic several neonatal conditions when patients are first seen by a neonatologist or any other pediatrician. This entity should be kept in mind in a newborn with the clinical features of sepsis, leukocytosis, thrombocytopenia, and huge hepatosplenomegaly. Infants with ALL are at high risk of treatment failure.

Keywords • Acute lymphoblastic leukemia • Neonatal leukemia • Cluster of differentiation

How to Treat Extramedullary Acute Lymphoblastic Leukemia

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Abstract

Isolated extramedullary acute myeloid leukemia as a myeloid sarcoma is expectable, whereas isolated extramedullary acute lymphoblastic leukemia—termed “B-lymphoblastic lymphoma (B-LBL)”—does not tally with all the definitions of acute lymphoblastic leukemia (ALL).

Purely or isolated extramedullary blast cell presentation is rare and often it is a unique presentation of AML or lymphoma with or without <25% blast in the bone marrow. Evolution of B-LBL with the sequential involvement of different extramedullary tissues such as the skin, dental tissue, and bone is unique and hitherto has been poorly described in ALL and lymphoid malignancies. Extramedullary ALL is a situation where lymphoblasts present at a non-routine extralymphatic structure (routine lymphatic structures such as bone marrow and lymph nodes) with bone marrow involvement from a minimal residual disease to an overt light microscopic disease. Samples of these conditions include gum hyperplasia, leukemia cutis, para-spinal leukemic mass, maxillary sinus mass, primary renal mass, osteopathy, and pancreatic mass as a leukemic infiltration. These patients should be treated with high-risk ALL chemotherapy protocols or anthracycline-based protocols. Radiation therapy may be useful. External beam is the type of radiation therapy used to treat ALL. During external beam radiation therapy, a machine directs radiation through the skin to the tumor and some of the tissue around it.

Keywords • Extramedullary acute leukemia • Acute lymphoblastic leukemia • B-lymphoblastic lymphoma (B-LBL) • Minimal residual disease

Management of Refractory/Relapsed Acute Leukemia Patients with Cardiac Limitation by Anthracycline-Free Chemotherapy Regimens in Pediatrics

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Abstract

Anthracycline-based treatment for acute leukemia can be associated with significant morbidity and mortality among pediatric patients or those with significant co-morbidities. Furthermore, for patients with previous anthracycline exposure or for those with preexisting cardiac diseases, administering a full dose of anthracycline poses an increased risk of cardiotoxicity.

There is moderate-quality evidence to support the use of FLAG (fludarabine, cytarabine, and filgrastim), ICE-rituximab regimens, monoclonal antibodies, or tyrosine kinase inhibitors such as sorafenib as non-anthracycline-based chemotherapy for relapsed/refractory acute leukemia and as initial therapy or clofarabine or cladribine for acute myeloid leukemia in patients for whom anthracycline-containing combination chemotherapy is inappropriate.

Keywords • FLAG • ICE • Rituximab • Anthracycline • Acute leukemia

MicroRNA-155 Induces Apoptosis in Human T-cell Leukemia Jurkat Cells via Targets Caspase Transcripts

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Abstract

Background: Caspase plays crucial roles in the induction of apoptosis. Previous studies have suggested that microRNAs (miRNAs) are also candidate molecules in the modulation of apoptotic pathways. Previous studies have demonstrated that miRNA-155 (miR-155) displays both apoptotic and anti-apoptotic functions in various cell lines. The present study aimed to examine the effects of miR-155 on the survival of Jurkat cells (a tumor T lymphocyte cell line) and its effects on the mRNA levels of caspases transcripts.

Methods: Jurkat cells were transfected with miR-155, as well as a scrambled sequence and mock as controls, using Lipofectamine 2000 commercial kit. The expressions of caspases transcripts were quantitated against beta-actin and GAPDH (as housekeeping genes) using real-time PCR technique.

Results: The results identified that the mRNA levels of caspase-2 and 10 were significantly increased following miR-155 transfection, while the expression of caspase-8 was decreased.

Conclusion: Based on the results, it is concluded that miR-155 can lead to apoptosis in Jurkat cells via upregulation of caspase-2 and 10 mRNAs. It seems that miR-155 induces apoptosis via extrinsic pathway.

Keywords • MicroRNAs • Apoptosis • Neoplasm

MicroRNA-143 Induces Apoptosis in Human T-cell Leukemia Jurkat Cells via the Regulation of Caspase Transcripts

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Abstract

Background: In humans, caspases play important roles in the induction of apoptosis. MicroRNAs (miRNAs) are also candidate molecules in the regulation of apoptotic pathways. Previous studies revealed that miRNA-143 (miR-143) induces apoptosis in cancer cell lines but its molecular mechanisms have yet to be clarified. The present study aimed to examine the mRNA levels of caspases transcripts in Jurkat cells following treatment with miR-143.

Methods: Jurkat cell was transfected with miR-143, as well as a scrambled sequence and vehicle controls. Transcript levels of caspases were determined and quantitated against beta-actin and GAPDH (as housekeeping genes) using real-time PCR technique.

Results: The results indicated that mRNA levels of caspase-2, 7, and 10 were significantly increased, while the expression of caspase-8 was decreased in the miR-143 transfected Jurkat cell line when compared to the scrambled sequence or vehicle only treated cells.

Conclusion: The data show that miR-143 leads to increased expression of caspase-2, 7, and 10 mRNAs but not caspase-8. The data suggest that miR-143 should be considered for futures studies as a potent inducer of apoptosis via the extrinsic pathway in human cancer cells.

Keywords • MicroRNAs • Apoptosis • Neoplasm

The CXC chemokines CXCL1, CXCL10, and CXCL12 are Differently Expressed Before and After Bone Marrow Transplantation in Acute Myeloblastic Leukemia Patients

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Abstract

Background: Chemokine is important in the development of leukemia. CXCL1, CXCL10, and CXCL12 are the chemokines involved in immune responses. The present study was designed to examine the serum levels of these chemokines in acute myeloblastic leukemia (AML) patients before and after bone marrow transplantation (BMT).

Methods: Samples were collected from 37 AML patients before and after receiving BMT, along with 50 controls. CXCL1, CXCL10, and CXCL12 concentrations were determined by ELISA. Demographic data were also collected by a questionnaire. Data were analyzed using t test, χ^2 , and ANOVA statistical methods by the SPSS statistical software (version 18.0).

Results: The results indicated that the elevated levels of CXCL12 in AML patients remained unchanged after transplantation. In contrast to CXCL12, the CXCL10 concentration was decreased in AML patients but was not different before and after BMT. All studied chemokines were elevated in BMT patients with a history of PLT but not packed cell transfusion. In BMT recipients who received BMT from siblings, both CXCL1 and CXCL10 were increased in comparison to patients who received BMT from parents while CXCL12 sustained unchanged in both groups. CXCL1 and CXCL10 were increased in acute and chronic GVHD patients in comparison to without GVHD.

Conclusion: According to the results, it can be concluded that CXC chemokines play important roles in the pathogenesis of AML and BMT. It is also worthy to note that chemokines could probably be used as diagnostic biological markers, as well as possible promising therapeutic targets.

Keywords • Acute myeloblastic leukemia • Chemokine CXCL1 • Chemokine CXCL10 • Chemokine CXCL12 • Bone marrow transplantation

Significant Downregulation of miR-128 in Childhood Acute Lymphoblastic Leukemia during Treatment

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Abstract

Background: Acute lymphoblastic leukemia (ALL) as a heterogeneous disease occurs in both children and adults. However, its incidence peaks between 2 and 5 years of age comprising several sub-entities that differ in both immunophenotypic and molecular characteristics. MicroRNAs (miRNAs) are small and non-coding RNA molecules involved in the regulation of gene expression, which can hybridize to target messenger RNAs and regulate their expression post-transcriptionally. MicroRNAs play a significant role in the development and progression of acute lymphoblastic leukemia (ALL). The present study aimed to estimate the associations between miRNAs and treatments in childhood acute lymphoblastic leukemia (ALL) to discover their role in the course of the disease.

Methods: The peripheral blood of 30 patients with ALL, under 18 years of age and sex-matched healthy control individuals, was used to evaluate the expression of miR-128 using real-time PCR. miRNA expressions associated with the diagnosis and outcome were prospectively evaluated.

Results: Significant downregulation was found between patients before and after treatment in total miR-128 expression during 6 months period.

Conclusion: miR-128 as a strong novel candidate oncogenic microRNA, not only could be mentioned as biomarkers in the diagnosis and monitoring of ALL, but also provide new insights into their potential roles in leukemogenesis. Further investigation with larger samples is recommended to demonstrate the role of miRNAs in leukemia clearly.

Keywords • Acute lymphoblastic leukemia • miRNAs • Real time PCR • Downregulation

Quantitative Expression of Toll-like Receptors 1 to 5 on Peripheral Blood Mononuclear Cells from Children with B-cell Acute Lymphoblastic Leukemia

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Abstract

Background: Toll-like receptors (TLRs) have a pivotal role in innate and adaptive immune responses and are involved in leukemia activation and progression. The expression and functionality of TLRs on leukemic cells have rarely been elucidated. The present study aimed to investigate the quantitative expression of TLR1, TLR2, TLR3, TLR4, and TLR5 by real-time PCR method on PBMCs from children (aged 1-14 years) with early precursor B-cell acute lymphoblastic leukemia (pro-B-ALL), precursor B-cell ALL (pre-B-ALL), and mature B-cell ALL.

Methods: Thirty-nine samples of B-cell acute lymphoblastic leukemia, confirm by flow cytometry parameter, were collected prior to any treatment. PBMCs were isolated by Ficoll density centrifugation and the expressions of TLR1, TLR2, TLR3, TLR4, and TLR5 were detected by the quantitative real-time PCR.

Results: The mean expression of TLR1 and TLR4 in Pre-B samples was higher than Pre-B and mature B patients. The mean of TLR2 expression was approximately the same in the three types of patients. In Pro-B subtype, the mean of TLR3 and TLR5 expression was higher than the two other types.

Conclusion: Although TLR1, TLR2, TLR3, TLR4, and TLR5 are expressed in B-cell acute lymphoblastic leukemia samples, our result did not show any significant difference between following TLRs expressions. In addition, the three phenotypes leukemia (Pro-B, Pre-B, and mature B) did not significantly differ in the above-mentioned TLRs, possibly because there was a broad distribution of expression and only a small number of patients with each ALL phenotype.

Keywords • Toll-like receptor • Leukemia • B-cell • Gene expressions

Role of MicroRNAs in the Incidence of Multiple Drug Resistance in Children with Acute Lymphoblastic Leukemia

Atefeh Zamani

Abstract

Hematological malignancies account for a significant percentage of cancers in the world. One of the most common types of malignancies is acute lymphoblastic leukemia (ALL). ALL is one of the major blood cancers in humans resulting from the excessive proliferation of lymphoid progenitor cells, thus giving rise to B-cell and T-cell lineages. It is the most common types of cancer in children. Multiple drug resistance (MDR) often leads to relapse in patients who initially respond to treatment. MDR simultaneous resistance to different chemotherapy drugs occurs with different chemical structures that have different mechanisms. Therefore, drug resistance is a major problem in the treatment of acute leukemia.

Changes in microRNA expression levels can also be effective on drug resistance. MicroRNAs (miRNAs) are small non-coding RNA molecules group that often negatively regulates gene expression at the post-transcriptional level. MicroRNAs are the specific medical purposes of overcoming MDR in hematologic malignancies. In recent years, many studies regarding the diagnosis and treatment of different types of blood cancer and other cancers have been conducted with the help of microRNA.

Keywords • Precursor cell lymphoblastic leukemia-lymphoma
• MicroRNA • Multiple drug resistance

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Taq1 Polymorphism (rs731236) of the Vitamin D Receptor Gene in Children with Acute Lymphoblastic Leukemia

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Abstract

Background: Acute lymphoblastic leukemia (ALL) is the most common childhood cancer. Studies have shown that ALL occurs as a result of genetic abnormalities. 1, 25-dihydroxyvitamin D₃, as a secosteroid hormone, plays an important role in different metabolic pathways. The normal function of vitamin D occurs via binding to a ligand-activated transcription factor (i.e., vitamin D receptor [VDR]). Therefore, genetic variation in VDR may lead to various disorders such as cancer. We aimed to investigate the rs731236 polymorphism of the VDR gene in children with ALL.

Methods: Genomic DNA was extracted from 50 children under 15 years old with ALL and 50 age-matched healthy children's whole blood. The genetic variation of each participant was detected using polymerase chain reaction and restriction fragment length polymorphism (PCR-RFLP) with taqI restriction enzyme. Statistical analysis was performed using SPSS, version 22, following the χ^2 test.

Results: The VDR gene polymorphisms were genotyped in a total of 50 individuals with ALL, compared with 50 normal children at a mean age of 5.2 3.4 years. No deviation was observed from the Hardy–Weinberg equilibrium in the genotypic distribution of the rs731236 ($\chi^2=0.25$, $P>0.05$). The genotype frequency of TT, Tt, and tt was 25, 15, and 10 in the case group and 21, 27, and 2 in the control group, respectively, which showed a significant difference between the 2 groups ($P=0.011$). The tt genotype showed a strong protective effect against ALL over Tt (OR=9, CI 95%: 1.74 to 46.59).

Conclusion: We determined the frequency of the Taq1 (rs731236) polymorphism in the VDR gene in the Zanjan population. We conclude that the genotype variation in the VDR gene may have an effect on ALL incidences.

Keywords • Acute lymphoblastic leukemia (ALL) • Single-nucleotide polymorphism (SNP) • Vitamin D receptor (VDR)

The Relationship between IDH1 Mutations on Response to Treatment and Prognosis in Adult Patients with non-M3 AML

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Abstract

Background: IDH1 enzyme catalyzes oxidative decarboxylation of isocitrate to α -ketoglutarate (α -KG). Acquired mutation in IDH1 gene changes its function and has a role in tumorigenesis. Recently, an IDH mutation was reported in brain tumors and AML patients. The present study aimed to assess the relationship between IDH1 mutations on therapeutic therapy and prognosis in adult patients with AML.

Methods: The study population consisted of 70 adult patients with de novo AML (range: 15-60 years). IDH1 mutation was determined by the PCR-RFLP technique. Clinical and biological data were collected from patients' medical records. Association between IDH mutation, response to therapy, and survival was analyzed using the SPSS software.

Results: The frequency of IDH1 mutations was 5.71% (n=4) and 75% of patients with IDH1 mutation had normal cytogenetic Karyotype. Fifty percent of IDH1-mutated cases were in M4 subgroup. The results showed that IDH1 mutations were significantly associated with age, gender, leukocyte count, and blast percentage. In addition, 50% of patients with IDH1 mutation were resistant to chemotherapy and did not achieve complete remission. There was a shorter overall survival (OS) in patients with IDH1 mutation compared to those with wild type ($P=0.005$). All patients with IDH1 mutation died before the second year after treatment.

Conclusion: IDH1 mutations adversely affected response to therapy and survival in adults AML patients can be used as a prognostic factor in AML patients. However, more studies are required for confirmation.

Keywords • Acute myeloid leukemia • IDH1 protein • Prognosis

Evaluation of Seven Genes Expression Involved in Myeloid Differentiation in Patients with De Novo Acute Myeloid Leukemia

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Abstract

Background: One of the most important cases of acute myeloid leukemia is an abnormality in the expression of important genes that are involved in differentiation. Among genes that appear to have key roles in myeloid differentiation, CEBPA has a key role in differentiation and is connected to other genes. Because of the relationship between these genes with differentiated pathways and the key importance of CEBPA, as well as its dysregulation in AML, the relationship between CEBPA and genes related to CEBPA has not been yet studied; according to a literature review. Herein, the role of alternation in differentiation CEBPA, IRF8, PU.1, GFI1, RUNX1, CALR, and LEF-1 in leukemogenesis has been studied.

Methods: Gene expression was evaluated by real-time PCR and $\Delta\Delta CT$ method in 96 AML patients and 18 healthy individuals.

Results: The data indicated that some of the genes involved in differentiation unexpectedly had overexpression. Among the genes, only LEF-1 (monocyte/granulocyte) and PU.1 (granulocyte differentiation) had down-regulation with respect to the healthy group.

Conclusion: Contrary to expectations, the involved genes in myeloid differentiation had overexpression in most cases and leukemogenesis was observed. These genes, when in malignancy, showed different behavior compared to the normal situation; such that some of these genes may lose their tumor-suppressor gene function and behave like oncogenes. Based on our observation, it is believed that some of these genes might have changed their role in malignancy process. Further studies would contribute to design new methods, monitoring program, and treatment.

Keywords • Differentiation • Acute myeloid leukemia • CEBPA • RUNX1 • PU.1 • CALR • GFI1 • IRF8 • LEF-1

The Role of Stem Cell Differentiation Factors in Leukemogenesis and Their Importance in Diagnosis and Treatment of Acute Lymphoid Leukemia

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Abstract

Acute lymphoid leukemia (ALL) is the most common type of childhood malignant neoplasia with a cure rate of 70-80%. ALL is a malignancy originated from T- or B-lymphoid progenitors that encompass 80% of childhood leukemia. The etiology of ALL is considered multifactorial. However, despite the significant progress in treatment, 20% of affected children undergo relapse. There is a growing body of evidence supporting that cancer cells share many similarities with embryonic stem cells (ESCs). Transcription factors, such as Oct4, Sox2, c-Myc, and Klf4 are critical for establishing and maintaining pluripotent cell identity. Reprogramming of these factors plays important roles in the development and progression of many cancers. These factors are translated into the four proteins implicated in the reprogramming of somatic cells into inducible pluripotent cells (iPS) and aberrantly expressed in human leukemia. The present review study aimed to elucidate the differential expression patterns of Oct4, Sox2, c-Myc, and Klf4 genes in leukemia and evaluates its probable prognostic or diagnostic value for ALL. Finally, advances made on the application of Oct4, Sox2, c-Myc, and Klf4 and their impact on the diagnosis and treatment of acute lymphoblastic leukemia is summarized and discussed.

Keywords • Acute lymphoid leukemia • Stem cell factors • Embryonic stem cells

Downregulation of Survivin Concomitant with Induction of Apoptosis in NB4 Leukemia Cells by 9-tBAP from Spiro-Aminopyrimidone Family

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Abstract

Background: It has been recently reported that the activity of aminopyrimidone family induces apoptosis in human cancer cells. Herein, an active compound from spiro-aminopyrimidone family with apoptotic activity against NB4 acute promyelocytic leukemia cells is reported.

Methods: The cells were seeded in 96-well plates at 1×10^5 cells/well and treated with 10-150 μM of the 2,4-Diamino-1,3-diazaspiro [5.5]-9-tert-butyl-2,4-diene-5-carbonitril (9-tBAP). This compound was found to be a highly active cell growth inhibitor with IC_{50} of $30 \pm 3.5 \mu\text{M}$, as determined by MTT assay. Apoptosis, as the mechanism of cell death, was investigated morphologically by Hoechst 33258 staining, as well as quantitatively by annexin V/PI double staining. Evaluation of survivin expression in NB4 cells treated with 9-tBAP was performed by real-time PCR.

Results: The results of fluorescence microscopy and flow cytometry indicated that NB4 cells underwent apoptosis upon a single dose (at IC_{50} value) of the compound. In addition, apoptotic cell population increased by more than 60% following 72 hours treatment. Furthermore, real-time PCR analysis revealed that the treatment with the compound downregulated the expression of survivin in a time-dependent manner.

Conclusion: The presented data further suggest that 9-tBAP may provide a novel therapeutic approach for the treatment of leukemia.

Keywords • Survivin • 9-tBAP • NB4 Cells

MicroRNA-155 Induces Apoptosis in the Jurkat Cell Line via BCL2 Family Molecules Dependent Manner

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Abstract

Background: Apoptosis is described as a normal cell death program, which is regulated by several transcripts including BCL2 family members. MicroRNAs (miRNAs) are key regulators for the expression of apoptotic pathways. Previous studies have shown that miRNA-155 (miR-155) exhibits either apoptotic or anti-apoptotic functions in various cell lines. The present study aimed to evaluate the effects of miR-155 on the survival, as well as mRNA levels of BCL2 family molecules in Jurkat cells, a leukemic T-cell line.

Methods: MiR-155, a scrambled sequence, and PBS were introduced to Jurkat cells using Lipofectamine 2000 commercial kit. The expressions of BCL2 family transcripts and quantitated against beta-actin and GAPDH (as housekeeping genes) were measured using real-time PCR technique. The t test (SPSS software version 18.0) was used for the statistical analysis of data. $P < 0.05$ were considered as statistically significant.

Results: The results showed that mRNA levels of BCL2L2, BCL2A1, and MCL1 were significantly decreased, and inversely mRNA levels of Bak and Bik were significantly increased in miR-155 transfected Jurkat cells in comparison to both control groups.

Conclusion: miR-155 can induce apoptosis in Jurkat cells, either by upregulation of pro-apoptotic or downregulation of anti-apoptotic members of the BCL2 family.

Keywords • MicroRNAs • Apoptosis • Neoplasm

Assessment of Angiogenesis Status in Acute Myeloid Leukemic Patients from Diagnosis to post-Hematopoietic Stem Cell Transplantation

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Abstract

As already proven in solid tumors, increased angiogenesis leads to an increased number of blood vessels, resulting in unfavorable outcomes and resistance to chemotherapy. It was previously thought that angiogenesis plays no role in the pathogenesis of acute myeloid leukemia (AML) because AML is a liquid tumor. However, a large number of studies have suggested that increased angiogenesis has important roles in AML patients, including increased numbers of vessels in the bone marrow and pro-angiogenic factors, as well as decreased anti-angiogenic factors. Also a large number of studies have demonstrated that a 2-way communication is established between leukemic and endothelial cells, as a component of the vessel wall, in the bone marrow of AML patients. These 2 cells support the survival and proliferation of each other through the paracrine pathway, resulting in resistance to chemotherapy. In addition, it is well-established that increased angiogenesis is associated with unfavorable prognosis, lower survival, resistance to chemotherapy, and relapse. Furthermore, increased angiogenesis affects the response to treatment, hematopoietic stem cell transplantation (HSCT) outcome, and graft versus host disease occurrence. In this regard, this review will address vascular endothelial growth factor (VEGF) and angiopoietin (Ang), 2 of the most important angiogenic factors, in AML patients before and after HSCT. By increasing our understanding of the role of endothelial cells and angiogenic factors in AML patients from diagnosis to post transplantation, new therapeutic strategies can be developed to reduce angiogenesis, improve patients' survival, and reduce transplantation complications.

Keywords • Acute myeloid leukemia • Angiogenesis • Vascular endothelial growth factor • Endothelial cell • Hematopoietic stem cell transplantation

Acute Lymphoblastic Leukemia Phenotype Characterization of Iranian Patients

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Abstract

Background: Although the antigen expression patterns of acute lymphoblastic leukemia (ALL) are well known, the present study aimed to evaluate commonly used immune markers for immunophenotyping of acute leukemia to set the required minimum of diagnostic panels by flow cytometry.

Methods: A total of 89 the patients were evaluated. These patients referred from all over the country to the Iranian Blood Transfusion organization (Tehran, Iran) during 2013-2015. We compared the immunophenotype patterns of childhood and adult ALLs, including 69 (77.5%) B-ALL, 2 (2.2%) mature B.ALL, and 18 (20.2%) T-ALL cases using flow cytometry with broad antibody panel.

Results: CD19 and CD79a were the most frequent markers for B-ALL while CcD3, CD7, and CD5 were the most frequent antigens for T-ALL. TdT+/CD34+ was significantly higher in adult B-ALLs than children, which indicate blast cells are more immature in adults. In addition, CD10 and cCD79a were significantly higher in children with B-ALL, similar to CD5 and CD8 in children with T-ALL ($P<0.05$).

Aberrant phenotypes, including CD13, CD33, CD7, and CD117 were found in 7 (10.1%) B-ALL cases. These phenotypes were CD10, CD117, HLA-DR, and CD33 in 7 (38.9%) T-ALL cases. The expression of CD117 aberrant myeloid antigen was significantly and more frequently associated with T-ALL than B-lineage ALL ($P=0.02$).

Conclusion: Significant differences in antigen expression patterns between adult and pediatric ALL have been demonstrated in Iranian patients. Future studies would allow us to correlate specific markers with recurrent cytogenetic abnormalities and prognosis with therapeutic response.

Keywords • Acute lymphoblastic leukemia • Immunophenotyping • Flow cytometry

Causes of Early Deaths in Children with Acute Lymphoblastic Leukemia: A Systematic Review

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Abstract

Background: The rate of early death in acute lymphoblastic leukemia (ALL) is about 1%. The present study aimed to determine the major causes of early death in ALL and consequently increase the survival rate.

Methods: Databases such as PubMed, EMBASE, ScienceDirect and Google Scholar were searched for all relevant publications from 1975 to 2016. The keywords used in the search were acute lymphoblastic leukemia, early mortality, early death, and death in the induction phase. The inclusion criteria were all studies on the etiologies of early mortality in children with acute lymphoblastic leukemia. Early death means that death occurs before remission or within 30 days from the start of induction chemotherapy.

Results: A total of 12 studies fulfilled the inclusion criteria and 7,561 children under 18 years of age were studied. Among these, 354 patients died in the induction phase of therapy. The early mortality rate was 4.7%. The most common cause of early death was infection (52.5%), which was mainly bacterial. The second leading cause was bleeding (15%), frequently reported brain hemorrhage, and tumor lysis syndrome (4%) was the third most common cause. Other causes were septic shock (2%), hyperleukocytosis (2%), encephalopathy (1.7%), cardiomyopathy (1.7%), chemotherapy-related toxicity (1.2%), and thrombotic events (0.6%).

Conclusion: Children with ALL need more advanced supportive care mainly focused on strategies to prevent infection and bleeding, which was the most common causes of early deaths.

Keywords • Early deaths • Acute lymphoblastic leukemia • Early mortality

FMS-like Tyrosine Kinase 3 and Nucleophosmin 1 in Iranian Adult Acute Myeloid Leukemia Patients with Normal Karyotype

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Abstract

Background: The present study aimed to evaluate the frequency of FMS-like tyrosine kinase 3 (FLT3-ITD and FLT3-TKD) and nucleophosmin 1 (NPM1) mutation in Iranian cytogenetically normal acute myeloid leukemia (CN-AML) patients. In addition, the clinical and laboratory characteristics were compared between wild type and mutant patients.

Methods: Seventy newly diagnosed de novo AML patients were recruited at the time of diagnosis prior to chemotherapy achievement in which 54 had CN-AML. FLT3 and NPM1 genes were first amplified by polymerase chain reaction (PCR) method followed by direct sequencing.

Results: The frequency of FLT3-ITD, FLT3-TKD, and NPM1 mutations in CN-AML patients was 25.9%, 5.9%, and 20.8%, respectively. In addition, the most frequent NPM1 mutant type was the type-A mutation. FLT3-ITD mutation was more frequent in non-M3 patients compared to M3. No mutation was observed in both FLT3-TKD and NPM1 genes in patients with M3 FAB groups. There were no significant differences in mean WBC and platelet count, serum Hb level and bone marrow blast percentage of patients with wild type and mutant FLT3-ITD, as well as NPM1 genes. No difference was observed in the frequency of FLT3-ITD and NPM1 mutation regarding age and gender.

Conclusion: Given the high stability of NPM1 during the disease course, it can be used in combination with FLT3 and other known genetic markers to monitor patients especially for minimal residual disease (MRD) detection.

Keywords • Acute myeloid leukemia (AML) • Gene mutation • FMS-like tyrosine kinase 3 (FLT3) • Nucleophosmin 1 (NPM1)

Mutation of the Epigenetic Factors DNMT3A and IDH 1/2 in Iranian Acute Myeloid Leukemia Patients with Normal Karyotype

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Abstract

Background: Mutation of the genes encoding DNA methyltransferase 3A (DNMT3A) and isocitrate dehydrogenase 1/2 (IDH 1/2) are among the most commonly occurring mutations found in AML patients. The present study aimed to investigate the frequency of DNA methyltransferase 3A (DNMT3A) and isocitrate dehydrogenase 1/2 (IDH 1/2) mutations, as well as the clinical features of Iranian cytogenetically normal acute myeloid leukemia (CN-AML) patients harboring these mutations.

Methods: Thirty-nine CN-AML patients were recruited at the time of diagnosis prior to chemotherapy treatment. PCR followed by direct sequencing method was used to detect the mutations of DNMT3A (R882), IDH1 (R132), and IDH2 (R140 and R172).

Results: Of all CN-AML patients, DNMT3A, IDH1, and IDH2 mutations were observed in 5 (12.8%), 5 (12.8%), and 5 (13.2%), respectively. In addition, the most frequent DNMT3A, IDH1, and IDH2 mutant types were R882C, R132C, and R172K types, respectively. The results also showed that both DNMT3A and IDH1/2 mutations were not associated with a significant change in hemoglobin (Hb) levels, white blood cell (WBC), platelet count, and bone marrow blast percentage ($P>0.05$). There was also no significant difference in mutation status of DNMT3A and IDH1/2 genes regarding age and gender ($P>0.05$). A positive relationship was observed between the co-occurrence of DNMT3A and IDH1 ($P=0.05$), DNMT3A and IDH2 ($P=0.021$), and FLT3-ITD and NPM1 ($P=0.044$).

Conclusion: Taken together, DNMT3A and IDH1/2 genes can be used alongside other molecular markers like FLT3 and NPM1 for risk stratification and predicting clinical outcome, especially monitoring minimal residual disease (MRD) of CN-AML patients.

Keywords • Cytogenetically normal acute myeloid leukemia (CN-AML) • DNA methyltransferase 3A (DNMT3A) • Isocitrate dehydrogenase 1/2 (IDH 1/2) • Mutation

Necessity of ATP-Binding Cassette Gene Expression Profiling in Children with Acute Lymphoblastic Leukemia: Unsolved Challenges through Multidrug Resistance

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Abstract

Multidrug resistance (MDR) is known as a major issue among patients with malignancies. ATP-binding cassette (ABC) transporters are membrane-bound proteins that relate to the phenomenon of drug resistance. Forty-nine ABC genes categorized in 8 subfamilies (A–H) participate in the movement of chemotherapy agents across the cellular organelle membranes.

Comprehensive reviews have revealed that ABC transporters could be allied to chemotherapy failures due to drug-efflux capabilities. Some of the ABC transporters export endogenous agents in normal hematopoietic progenitors.

However, there is a link between MDR phenotypes caused by the gene expression of ABC transporters and the clinical outcome of patients with acute lymphoblastic leukemia (ALL). This link can be based on the induction and loss of gene expression through ABC transporters. The profile of the expression of ABC transporters in patients with ALL can be associated with poor response to therapy.

An electronic peer review article search was performed systematically to obtain the relevant literature with the CINAHL and PubMed databases. The keywords included ATP-binding cassette, multidrug resistance, cancer, leukemia, and pediatrics.

This comprehensive literature review was designed because there was no unique report on the expression profile of ABC transporters in children with ALL. The results of this study could be effective in future planning to improve MDR in children with ALL.

Keywords • ATP-binding cassette transporter • Leukemia • Multidrug resistance • Pediatrics

2-NDC from Dithiocarbamates Enhances ATRA-Induced Apoptosis in NB₄ Acute Promyelocytic Leukemia Cells

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Abstract

Background: All-trans-retinoic acid metabolites have been considered as an efficient therapeutic agent for acute promyelocytic leukemia (APL). Dithiocarbamate family is also known as important chemical synthetic compounds in cancer therapy.

Methods: The present study aimed to evaluate the growth inhibition and induction of apoptosis in NB₄ cells by 2-Nitro-1-Phenylethylpiperidine-1-carbodithioate (2-NDC) from dithiocarbamate family, and in combination with ATRA. The NB₄ cells were cultured and treated in 10-120 μ M of the compound for 24-72 hours. The percent of cell viability and growth inhibition was assessed by MTT assay. To evaluate the combinational effect of 2-NDC and ATRA, NB₄ cells were treated with 1-2 μ M of ATRA and 20 μ M of 2-NDC for 24-72 hours.

Results: 2-NDC inhibited viability with IC₅₀ of 20 μ M. Growth and proliferation of the cells were diminished by more than 85% and cell viability was decreased by about 70% upon 72 hours of treatment with 2-NDC and ATRA. Studies of flow cytometric annexin V/PI assessment and morphological changes by fluorescence microscopy also showed that 2-NDC induced NB₄ cell apoptosis at their respective IC₅₀ values after 24-72 hours of treatment.

Conclusion: It is confirmed that 2-NDC associated with ATRA can be a good candidate for further evaluation of leukemia treatment.

Keywords • Acute promyelocytic leukemia • All-trans-retinoic acid • Dithiocarbamates

Prooxidant-Antioxidant Balance in Iranian Veterans Exposed to Mustard Gas and its Correlation with Biochemical and Hematological Parameters

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Abstract

Background: The serum prooxidant-antioxidant-balance (PAB) was evaluated in sulfur mustard (SM)-exposed Iranian population more than 20 years after exposure by PAB assay.

Methods: In the present study, 42 SM-exposed and 30 unexposed (as controls) participants were recruited. PAB, biochemical, and hematological parameters were measured. The correlations of PAB with biochemical and hematological parameters were determined.

Results: The mean PAB value in the patient group (82.5 ± 34.8 HK) was significantly higher than the healthy group (47.5 ± 17.8 HK) ($P < 0.001$). The results demonstrated that in the patient group, PAB values have positively correlated with alkaline phosphatase. Furthermore, the PAB values showed a significant negative correlation with hepatic enzymes (AST, ALT), triglycerides, total bilirubin, and mean corpuscular hemoglobin concentration. The PAB values showed a marginally significant negative correlation with uric acid.

Conclusion: Potential late complications of past SM exposure may lead to oxidative stress. Hence, an increase in oxidative stress and alteration of biochemical and hematological parameters may be a consequence of the frequent respiratory infections rather than direct toxic effects of SM.

Keywords • Mustard gas • Biochemical and hematological parameters • Oxidative stress

Evaluation of Hematologic Parameters and Biochemical Markers of Iron Status in Metabolic Syndrome X Patients and a Control Group

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Abstract

Background: Metabolic syndrome X (MS) is a cluster of risk factors that raise the chance of developing type 2 diabetes and other disorders. High red blood cell count and iron overload have been suggested as possible causes for liver and cardiovascular events in patients suffering from MS. MS consists of a group of numerous physiological and metabolic abnormalities, including impaired glucose regulation, dyslipidemia, hypertension, and obesity.

Methods: A total of 385 individuals (176 subjects with and 209 subjects without MS) according to the International Diabetes Federation (IDF) criteria were recruited. Hematological parameters and biochemical markers of iron status were determined in the MS patients and the healthy controls using standard methods.

Results: Correlation between the hematologic parameters and the biochemical markers of iron status with MS in an Iranian population showed a significant association between MS and the indices of iron status. The subjects in the MS group had considerably higher levels of iron and ferritin than the control group. Also, RBC exhibited a significant correlation with MS.

Clinical finding concludes that iron likely plays a role in the pathogenesis of insulin resistance. This hypothesis has been noted in clinical studies, including those determining a relation between iron stores and increased ferritin and insulin resistance and amelioration of insulin resistance after iron depletion therapy.

Conclusion: Subjects with MS exhibited elevated RBC, ferritin, and iron concentrations.

Keywords • Metabolic syndrome X • Hematologic • Iron

Assessment of the Relationship between Serum Bicarbonate Levels and Hemoglobin in Hemodialysis Patients

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Abstract

Background: Anemia is a common complication of end-stage renal disease (ESRD) with different etiologies. Metabolic acidosis, a common condition particularly in ESRD patients, results in malnutrition, inflammation, and oxidative stress. The aim of the present study was to determine the relationship between predialysis serum bicarbonate levels and hemoglobin in patients under hemodialysis.

Methods: In this cross-sectional study, we analyzed data from patients who had been on hemodialysis for at least 6 months. Blood samples for serum bicarbonate concentrations, hemoglobin, iron level, ferritin, and total iron binding capacity were withdrawn before dialysis. The Pearson correlation analysis was used to determine the correlation between the variables.

Results: A total of 53 patients (29 males and 24 females), at a mean age of 44.67 ± 18.38 years, were included in this study. The Pearson correlation analysis showed that the values of predialysis serum bicarbonate levels correlated positively with age ($r=0.355$, $P=0.009$), hemoglobin ($r=0.44$, $P=0.02$), serum ferritin ($r=0.293$, $P=0.033$), and serum creatinine ($r=-0.508$, $P=0.001$).

Conclusion: This study found a weak positive association between hemoglobin and bicarbonate levels in hemodialysis patients. These findings indicate that in hemodialysis patients, acidosis may contribute to anemia, another common condition and a risk factor for a poor outcome.

Keywords • Bicarbonate • Hematologic test • Hemoglobin • Renal dialysis

Prognostic Significance of Receptor Tyrosine Kinase Gene Mutations in Adult Patients with Newly Diagnosed Acute Myeloid Leukemia

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Abstract

Background: Acute myeloid leukemia (AML) is a neoplastic disease that is developed by the uncontrolled clonal proliferation of neoplastic myeloid precursor cells and accumulation in the bone marrow of blasts which are progenitor hematopoietic cells with impaired or arrested differentiations. AML is the most common adult leukemia and is the most common cause of leukemia death. One of the essential events in leukemogenesis is disordered cell growth and upregulation of cell survival genes. The most common of these activating events are observed in the RTK Flt3, N-Ras, K-Ras, and Kit genes.

Methods: In this study, we evaluated the mutation rates of common known mutations of the above genes in 130 newly diagnosed AML patients. We used PCR-RFLP and direct sequencing to study Flt3 mutations, PCR and capillary electrophoresis as well as direct sequencing for the detection of Kit mutations, and direct sequencing for N-Ras and K-Ras mutations. Overall survival was used as the indicator of prognosis. We used the Kaplan–Meier analysis for survival analysis.

Results: The mutation rates for Flt3-TKD, Flt3-ITD, N-Ras, and K-Ras were 5.1%, 25%, 7%, and 5%, respectively. We did not find any mutation in KIT–ex 8 and KIT-exon 17. The survival analysis showed a statistically significant decrease in survival in the patients with Flt3-ITD mutation ($P=0.013$).

Conclusion: Mutation analysis can help predict the prognosis in AML patients and guide therapy approaches.

Keywords • Acute myeloid leukemia • Somatic mutations • Cell survival • FLT3 • RAS

Hematohidrosis: Report of Two Cases and Review of the Literature

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Abstract

Hematohidrosis is a clinical condition in which the afflicted individual sweats blood under situations of extreme physical or emotional stress. Hematohidrosis may be associated with bloody otorrhea and bloody lacrimation. There is a spontaneous painless bleeding through the unbroken skin in any part of the body or from salivary, lacrimal, or perifollicular sweat glands. The diagnosis is confirmed by observation of health professionals and the presence of blood components on the biochemistry studies of the discharge. Herein we introduce 2 patients with hematohidrosis. They had a partial initial response to propranolol, but they went on to have complete recovery after starting psychoanalysis and antianxiety medications.

Keywords • Body fluids • Sweat gland • Psychological stress
• Propranolol

The Knowledge of Pregnant Women on Iron-Deficiency Anemia: A Cross-Sectional Study

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Abstract

Background: Anemia is one of the most important nutrition and health disorders in the world. The most common blood disorder during pregnancy is anemia, especially due to iron deficiency that causes significant complications for the mother and fetus.

Methods: In a cross-sectional study, 400 pregnant women who attended the Gynecology Clinic of Yasuj (Iran) during fall 2016 were randomly selected. A questionnaire, with proven validity and reliability, was used for data collection. The descriptive statistics indexes, chi-square test, and independent *t* test were used for data analysis using the SPSS software.

Results: The mean age of women was 26.7±5.64. Among the patients, 80.75% regularly used iron supplement. Their knowledge level on contraceptive methods and iron-deficiency anemia was “well” (51.75%), causes of anemia was “well” (55.75%), symptoms of anemia was “average” (35.5%), complications of anemia was “poor” (46.25%), and prevention methods was “good” (51.75%).

Conclusion: Based on our findings, a training on the importance of anemia during pregnancy for this group of patients with iron-deficiency anemia is strongly recommended.

Keywords • Pregnant • Anemia • Iron • Deficiency

Prolonged Activated Partial Thromboplastin Time in Patient without Bleeding Disorder: A Case Report

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Abstract

High-molecular-weight kininogen (HMWK), also known as Fitzgerald factor and Williams factor, is a cofactor involved in the kinin-kallikrein system that speeds up the intrinsic coagulation pathway. HMWK deficiency is a rare autosomal recessive trait found with the elevation of activated partial thromboplastin time (aPTT). HMWK deficiency is negative for lupus anticoagulant and is not associated with bleeding. The present study aimed to describe a patient with HMWK deficiency with prolonged aPTT.

Case Presentation: A 76-year-old male was a candidate for cataract surgery. He was referred for laboratory test before surgery. He reported no underlying disease and coagulant drug usage. He had no history of bleeding disorders and no sign of hemorrhage at that time. CBC was normal and the results of coagulant tests were PT: 12.6 sec, aPTT: 115 sec, and INR: 1.0. Additional coagulant tests showed mixed aPTT: 33.2, factor XII: 85%, factor XI: 65%, factor IX: 122%, factor VIII: 85%, fibrinogen: 3.5 g/L, prekallikrein: 95%, and HMWK less than 1%. Finally, he was diagnosed with HMWK deficiency because this deficiency is a trait and causes no bleeding disorder. He underwent cataract surgery without any problems. HMWK deficiency is a trait that requires no treatment. Hence, consideration for the elevated aPTT value (with or without bleeding) or a history of bleeding disorders is required to make a right medical decision, diagnosis, and treatment.

Keywords • Kininogen • High-molecular-weight • Partial thromboplastin time • Hemorrhage

Effects of Exposure to Electromagnetic Fields of Mobile Phone Jammers on Hematological Parameters

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Abstract

Background: The rapid development of telecommunications technology, along with the application of mobile phones, creates problems such as the sound of ringing in places like conference rooms, libraries, lecture rooms, and mosques. An instrument called “GSM Jammer” can inhibit the use of mobiles by interfering with the cell phone signal. All phones within the effective radius of the jammer are silenced. We aimed to investigate the effects of jammer radiation on blood factors in male rats.

Methods: Sixty male rats were randomly divided into 6 groups. The 1st phase contained 30 immature and the 2nd phase included 30 adult rats. Each phase consisted of control, sham, and experimental groups, with each group containing 10 animals. Cages in the sham and exposure group were located at a 50-cm distance from the jammer device. The rats in the experimental group were exposed to turned-on radiation for 5 hours a day, 5 consecutive days per week for 40 days. The sham group was kept in an inactive exposure. The blood samples were taken from the heart, and blood factors, including blood cell count, hemoglobin level, hematocrit level, MCV, and MCHC, were measured and analyzed by SPSS, version 15.

Results: There was a significant difference between the blood factors, including PLT, MCHC, MCV, RDWCV, Hct, and Hb ($P \leq 0.05$), but there were no significant differences in the lymphocytes between the different groups.

Conclusion: According to the results of the present study, it can be concluded that the GSM Jammer exerts significant effects on the blood parameters of rats. It is suggested that further studies be conducted in this area to confirm the findings.

Keywords • Electromagnetic field • Radiation • Blood

Evaluation of the Flow for the Quantification of Fetomaternal Hemorrhage

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Abstract

Background: Quantification of the amount of fetal RBCs derived from fetomaternal hemorrhage (FMH) in the maternal circulation could be of importance to calculate an adequate dose of post-delivery anti-D-immunoglobulin in RhD-negative women. The present study aimed to evaluate direct immunofluorescence flow cytometry technique in artificial and clinical samples compared to Kleihauer-Betke test.

Methods: Blood samples from 26 pregnant women who were admitted in Hafez Hospital (Shiraz, Iran) for delivery were tested by the direct immunofluorescence flow cytometry and KBT techniques to determine the amount of FMH in the maternal circulation. The zone of D-positive cells was identified employing artificial samples, including 0.3, 0.6, 1, 1.5, 2, 5, 10, and 50 percent of D-positive fetal cell in D-negative maternal cells.

Results: The analysis of 26 clinical samples for FMH showed consistent quantification with the flow cytometry and Kleihauer techniques. Although a good correlation was found between the KBT and flow cytometry results, in artificial samples containing more than 2% of fetal RhD positive cells, the flow cytometry results were more close to theoretical percentages. In patients with FMH>4 ml, the FMH and consequently the required vial of Ig were overestimated using KBT.

Conclusion: The majority of the calculated FMH could have been neutralized by doses less than 625 IU, whereas the routine dose in Iran is more than double (1500 IU). This achievement demonstrates that adjustment between the RhDIg dose and FMH size is inevitable.

Keywords • Fetomaternal transfusion • Rho(D) immune globulin • Flow cytometry • Pregnancy • Fetus • Rh blood-group system

Delay in the Diagnosis of Thalassemia: Need for the Management of Thalassemia Programs

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Abstract

Background: Thalassemia is an important public health challenge worldwide with an estimated number of 330,000 newborns annually. Delay in diagnosis not only increases the morbidity and mortality rates, but also can lead to uncertainties about the success of the thalassemia prevention program (TPP). This study is the 1st of its kind to determine the delay in thalassemia diagnosis among this population.

Methods: This registry based cross-sectional study was conducted on 1,003 thalassemia patients in 2015 in Shiraz, Iran. Univariate and multivariate ordinal logistic regression models were used to assess the factors associated with delay.

Results: Of the 981 patients, 48.5% were female, 71.2% were thalassemia major, and 23.8% were death cases. The proportion of delay in diagnosis was observed among 64.9% of the patients, with the mean of 13.4 months (95% CI: 10.9 to 15.9).

Multivariate ordinal logistic regression showed that the girls (adjusted OR=1.32), and the death patients (adjusted OR=1.95) were more likely to have delayed diagnosis. There was an increasing trend of risk in delayed diagnosis associated with 1-year per birth cohort. The ORs were 1.0, 1.52, 1.55, and 2.22, respectively, for birth cohort 1980 and earlier, 1981 to 1990, 1991 to 2000, and 2001 to the present (P for trend = 0.014). In addition, the odds of delayed diagnosis in the thalassemia major patients were significantly 0.58 times lower than those with the thalassemia intermedia.

Conclusion: A high proportion of delayed diagnosis was found. This finding could justify the poor outcomes for thalassemia patients. Educational programs for the community and revising the TPP are required to the early detection of the disease.

Keywords • Delayed diagnosis • Thalassemia • Iran

Circulating Serum MicroRNA: An Early Biomarker of AML

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Abstract

Acute myeloid leukemia (AML) is a highly diverse disease characterized by various cytogenetic and molecular abnormalities. AML patients carry t(16;16), t(15;17), or t(8;21). MicroRNAs are small non-coding RNAs that show variable expression during myeloid differentiation. Recently, miRNAs have been demonstrated to be present in serum or plasma called circulating miRNAs, which could serve as noninvasive biomarkers for cancer detection. Furthermore, miRNAs are negative regulators of gene expression that play an important role in hematopoiesis; however, little is known about circulating miRNA profiles in AML patients. Such patients require immediate treatment to prevent interference with the production of healthy white blood cells in the bone marrow. Therefore, early diagnosis will be very useful.

A number of studies were selected from PubMed (MEDLINE), Google Scholar, and Scopus databases. In several studies, researchers employed high-throughput Illumina Solexa sequencing scan followed by qRT-PCR assay to investigate the profiles of serum miRNA expression in AML systematically and extensively. Many research groups have reported a close relationship between aberrant miRNA expression and the pathogenesis, diagnosis, and prognosis of AML. Serum samples are easily acquired in a relatively noninvasive manner and isolated miRNAs are readily detected by qRT-PCR. Therefore, the determination of serum miRNA profiles in AML patients is quite meaningful. The qRT-PCR identified six serum miRNAs, namely miR-10a-5p, miR-93-5p, miR-129-5p, miR-155-5p, miR-181b-5p, and miR-320d whose concentrations were significantly upregulated in the serum of AML patients compared with normal controls.

Keywords • Acute myeloid leukemia • Serum microRNA • Biomarker

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Improving Medical Intelligent Messaging in Controlling and Recovery from Iron Deficiency Anemia

Taybe Shahraki

Abstract

Background: The application of mobile decision support system is becoming an essential part of the healthcare system. The present study aimed to introduce the role of “smart instant messenger” in optimizing the process control and recovery of patients with iron deficiency anemia.

Methods: A collection of personal information data was gathered and entered into the medical and health smart decision system. The results were reviewed and analyzed towards designing a system on Android platform based on Java programming language. The SQL database monitoring (Lite) tool in combination with Microsoft Excel was used to compare the population.

Results: The smart mobile decision support system is only applicable to patients. It is an effective and efficient system in medical fields, mobile health-conscious, and self-care.

Conclusion: The application of intelligent decision support systems in the field of healthcare and implementation of mobile health would reduce treatment duration and costs to the healthcare system. It improves doctor-patient interaction by saving time and provides instant communication between them.

Keywords • Mobile health • Mobile technology • Mobile equipment • Intelligent messaging systems

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Comparison of Hematimetric Findings and Blood Varieties Zinc and Copper between Children with Giardiasis and Healthy

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Abstract

Background: Giardia lamblia infection is a common cause of food- and water-borne diarrhea in non-sanitary communities. The most important vital trace elements in the human body are copper and zinc. Zinc is necessary for the immune system functions and copper is essential for the production of red blood cells. The present study aimed to exhibit a comparison of hematimetric findings and blood varieties zinc and copper between children with giardiasis and healthy children.

Methods: The study was carried out on 30 children with giardiasis and 30 healthy children as the control group. The hematological examination and trace elements assay was performed. The data were analyzed using the SPSS statistical software (version 19.0). A chi-square test was used for data analysis of qualitative variables and values were compared using the independent *t* test and Mann-Whitney exact test.

Results: The levels of MCHC ($P=0.027$) and neutrophils ($P=0.035$) decreased significantly in children with chronic giardiasis compared to healthy controls. The levels of RBC ($P<0.001$) and hematocrit ($P<0.001$) increased significantly in children with the chronic disease compared to controls. There was no significant difference in levels of hemoglobin, MCV, lymphocytes, MCH, leukocytes, and platelets between the two groups. Zinc levels in the study group were remarkably lower than the control group ($P=0.001$). In addition, there was a significant difference in serum copper levels between both groups ($P=0.003$).

Conclusion: Giardia infection significantly elevated the levels of RBC, hematocrit, and the serum copper levels in children with the chronic disease compared to healthy, while it decreased the serum zinc.

Keywords • Hematimetric findings • Giardia lamblia • Zinc • Copper

Gelatinase-A Expression Profile in Human Leukemic Cells

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Abstract

Background: Gelatinases are a big group of enzymes belonging to the matrix metalloproteinases (MMPs) family. MMPs are wide-ranging endopeptidases, which degrade the extracellular matrix and play a pivotal role in tumor invasion, metastasis, and angiogenesis. The important role of angiogenesis in leukemia has been reported in many investigations. The present study aimed to evaluate the expression profile of gelatinase-A (MMP-2) in two human leukemic cell lines in vitro.

Methods: Human leukemic monocyte (U937) and T (Molt-4) cells were cultured in a complete RPMI-1640 medium. Then, the cells at logarithmic growth phase were seeded at a concentration of 10^6 cells/ml and incubated with different concentrations of phorbol myristate acetate (PMA) (25 ng/ml) or phytohemagglutinin (PHA) (10 μ g/ml) for 24 hours. Next, the gelatinase-A activity in the cell culture supernates was evaluated by gelatin zymography.

Results: PHA/PMA significantly increased gelatinase-A activity in U937 and Molt-4 cells after 24 hours of incubation compared with untreated control cells.

Conclusion: The PHA and PMA are well inducers of gelatinase-A activity in human leukemic cells. In addition, human leukemic U937 and Molt-4 cells can potentially produce gelatinase-A. Thus, PHA or PMA that stimulates U937/Molt-4 cells could provide an appropriate system to study the mechanisms regulating gelatinases activity in leukemia as well as screening the gelatinases stimulators/inhibitors.

Keywords • Molt-4 • U937 • Leukemia • Gelatinase-A

Evaluation of Stability and Optimization of the Albumin-Free Recombinant Streptokinase Formulation

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Abstract

Background: One of the most important causes of mortality in the world is impaired blood flow due to blood clot formation. Primary prevention plays an important role in reducing deaths from heart disease and stroke. Streptokinase is a bacterial protein that is produced by β -hemolytic streptococci. The production of recombinant proteins such as streptokinase is particularly important due to their therapeutic applications. However, achieving a proper and safe formulation for therapeutic recombinant proteins has an influential role in their efficiency. Due to limited data and research about ways for formulating this kinase, in this study, the optimization of formulations and the stability of freeze-dried products containing recombinant streptokinase were studied.

Methods: Four formulations from recombinant streptokinase, containing albumin, glycine, glycine and mannitol, and mannitol (A, B, C, and D, respectively) were prepared. After characterizing the main quality attributes, we evaluated the formulations for their stability profile according to the ICH's guideline. For this purpose, the appearance, reconstitution time, pH, biological activity, purity, osmolality, peptide mapping, humidity, and particle counting analyses were performed in the predetermined schedules.

Results: Test results showed that formulation C was acceptable in terms of purity, moisture content, and biological activity.

Conclusion: A stable, efficient, and safe drug formulation requires the use of amino acids, carbohydrates, and polyols in recombinant streptokinase.

Keywords • Streptokinase • Freeze dry • Albumin

Prevalence of Anemia and its Risk Factors among Infants Aged 6-12 Months

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Abstract

Background: Anemia is one of the significant public health problems among children in the world and has serious consequences on their growth, development, and survival. The present study aimed to assess the prevalence of anemia and its risk factors in infants from Yasuj (Boyer-Ahmad, Iran) during 2016.

Methods: In a cross-sectional study, based on simple random sampling, a total of 202 rural infants aged 6-12 months were enrolled. Data collection (demographic and hemoglobin) was carried out through recorded files at health centers. Infants with hemoglobin \leq 11 mg/dl, according to routine complete blood count in 6-9 months of age, were considered anemic. Data were analyzed using the SPSS statistical software (version 22.0).

Results: The prevalence of anemia was 38.1% (28.7% mild, 9.4% moderate). Mean hemoglobin was 11.18 ± 0.95 . There was no significant difference in the prevalence of anemia in both sexes ($P=0.74$), different seasons of birth ($P=0.66$), weight at birth (\leq 2500 vs. \geq 2500 gr) ($P=0.47$), and gestational age at birth (\leq 37 vs. \geq 37 weeks) ($P=0.61$). However, it was significantly lower in breastfed infants in comparison with the formula feeding ($P=0.03$).

Conclusion: Given the high prevalence of anemia in rural infants (more than one-third) and its proven negative consequences on their cognitive and behavioral development even in later years, the need for implementing an effective intervention is apparent.

Keywords • Anemia • Infants • Prevalence • Iran

Evaluating Urinary Neutrophil Gelatinase-Associated Lipocalin as a Biomarker of Renal Function in Hematologic–Oncologic Patients Receiving Amphotericin B

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Abstract

Background: Serum creatinine, as a classic biomarker of renal function, has several drawbacks in clinical practice. Neutrophil gelatinase-associated lipocalin (NGAL) has been shown to be superior to serum creatinine in detecting acute kidney injury.

Methods: A cross-sectional study was performed over a 9-month period at 3 hematology–oncology wards. Patients aged equal to or above 15 years with no documented history of acute kidney injury or chronic kidney disease planned to receive any formulation of amphotericin B for at least 1 week were included. Serum creatinine, urine creatinine, and urine NGAL were determined at days 0, 3, 5, 7, 10, and 14 of amphotericin B treatment.

Results: Eleven out of 40 (27.5%) patients developed amphotericin B nephrotoxicity. There was no statistically significant correlation between urine creatinine and urine NGAL at the studied time points. The overall change in the mean values of urine NGAL was not statistically significant either within ($P=0.251$) or between ($P=0.545$) the 2 groups during amphotericin B treatment. The area under the curve of urine NGAL at day 0 for predicting amphotericin B nephrotoxicity was significantly higher than that of urine creatinine and serum creatinine ($P=0.01$).

Conclusion: Increasing pattern of urine NGAL was not statistically significant compared to the baseline values and was comparable between the patients with and without amphotericin B nephrotoxicity. The urine level of NGAL at the 1st day of starting amphotericin B was more accurate than serum and urine creatinine in predicting acute kidney injury caused by amphotericin B.

Keywords • Urine • Neutrophil gelatinase-associated lipocalin
• Amphotericin B • Nephrotoxicity

Prevalence of G6PD Deficiency in Children Aged 2-12 Years

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Abstract

Background: Glucose-6-phosphate dehydrogenase deficiency (G6PD deficiency) is an X-linked recessive inborn error of metabolism, due to which about 400 million people are affected worldwide. Neonatal jaundice, drug-induced hemolysis, beans, hemolysis are caused by the infection from a deficiency of this enzyme. The prevalence of G6PD deficiency varies in diverse population groups and different countries. G6PD deficiency had resulted in 4,100 deaths in 2013. The present study aimed to determine the frequency of G6PD deficiency in children, aged 2-12 years, who referred to Pars Laboratory (Tehran, Iran).

Methods: The present cross-sectional study was conducted on 624 people. The study populations of children aged 2-12 years referred to Pars Laboratory for which sampling was performed in one-step. Enzyme activity was tested by fluorescent stain. Data were analyzed using the SPSS software. For comparing enzyme deficiency, we used chi-square test between male and female categories.

Results: From the total of 624 children, 256 children (41.02%) were male and 368 (58.98%) were female. G6PD deficiency was 35.18% in males and 2.44% in females, which showed a significant difference ($P < 0.0001$). Furthermore, the relative risk (OR) of G6PD deficiency in males was 8.97 against females (CI=4.30-18.67).

Conclusion: The prevalence of G6PD deficiency in male children was higher and showed a significant difference ($P < 0.0001$). However, the result requires additional screening test on all newborns after birth, particularly in males. A comprehensive national program for the prevention of its complications is recommended.

Keywords • Glucose-6-phosphate dehydrogenase deficiency • Prevalence • Screening test

Outcomes of Autologous Stem Cell Transplantation with CEAM Conditioning in Relapsed or Refractory Hodgkin's Lymphoma

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Abstract

Background: Despite the generally excellent prognosis of children and adolescents with Hodgkin's lymphoma, approximately 20% of the patients relapse. High-dose chemotherapy, followed by autologous stem cell transplantation (ASCT), is a recognized treatment option for patients with relapsed Hodgkin's lymphoma. This study evaluated the results and outcome of non-cryopreserved autologous stem cell transplantation of 32 patients with Hodgkin's lymphoma.

Methods: Thirty-two patients, aged between 4 and 25 years (median=13.5 y, M/F=20/12), with relapsed, refractory, or poor prognosis Hodgkin's disease underwent ASCT in our hospital (from 2012 to 2016). Status at transplantation was: 2nd complete remission in 16, further complete remission (complete remission >2) in 13, and partial remission in 3. All the patients received chemotherapy-based conditioning regimens: cyclophosphamide, carmustine, and etoposide (CBV): 6, CCNU (200 mg/m²) day -3, etoposide (800 mg/m²) days -3 and -2, cytarabine (1000 mg/m²) days -3 and -2, and melphalan (140 mg/m²) day -1 (CEAM). The peripheral blood of 24 patients was the source of progenitor cells in the 32 patients.

Results: The median mononuclear cell dose was 5.5×10⁸/kg. The median time to reach an absolute neutrophil count greater than 0.5×10⁹/L was 13 days, and the median time to a platelet count greater than 20×10⁹ was 16 days. Transplantation-related mortality at 100 days did not occur. With a median follow-up of 39 months (4–48 mon) after transplantation, the event-free survival rate was 84%.

Conclusion: High-dose therapy with stem cell rescue can lead to durable remissions in children and adolescents with advanced Hodgkin's disease. Our analysis suggests that these regimens (CEAM and CBV) are feasible in pediatric patients with acceptable engraftment.

Keywords • CEAM • Children • Hodgkin's lymphoma

Lipid Profile in Patients with Lymphoid Hematologic Malignancy

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Abstract

Background: Diet and obesity are recognized as important risk factors for cancer development and progression. Hypercholesterolemia facilitates lymphoma lymphoblastic cell growth and tumor progression. The present study aimed to evaluate the lipid profile in patients with hematologic lymphoid malignancy.

Methods: A total of 200 patients, with lymphoid hematologic malignancy and median age 48.65 ± 18.69 , were enrolled. The underlying hematologic malignancy included Hodgkin's lymphoma, non-Hodgkin's lymphoma, chronic lymphocytic leukemia, multiple myeloma, and acute lymphocytic leukemia. The total cholesterol, triglyceride, low-density lipoprotein, and high-density lipoprotein were measured.

Results: The highest cholesterol value was seen in multiple myeloma (212 ± 63 mg/dl) and the lowest rate was seen in Hodgkin lymphoma (168 ± 35.1 mg/dl) ($P=0.004$). The result of triglyceride serum levels was the same as cholesterol. The highest level was in myeloma (234 ± 146.4 mg/dl) and the lowest level in Hodgkin lymphoma (130 ± 63.35 mg/dl) ($P=0.007$). In comparing HDL serum level, we observed the highest level in ALL (48 ± 14.1 mg/dl) and the lowest in multiple myeloma (41 ± 6.9 mg/dl), which was not statistically significant ($P=0.6$). For the serum LDL level, the difference was not significant nor meaningful.

Conclusion: Cholesterol reducing agent in myeloma can induce apoptosis and is promising. The highest cholesterol level was seen in multiple myeloma. In addition, the level of HDL in multiple myeloma patients was lower than the other lymphoid malignancy. The lowest serum cholesterol and triglyceride serum levels were seen in Hodgkin lymphoma. It could be due to the lower median age and the underlying disease. Smaller differences were observed for lipid profile in lymphoid hematologic malignancy and these changes are more significant in multiple myeloma patients.

Keywords • Lipid • Lymphoid • Hematologic

Evaluation of MicroRNA Expression in Formalin-Fixed Paraffin-Embedded Tissue of against Controls

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Abstract

Background: Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma (NHL) in that it accounts for 40% of all NHL patients. Lymphoma, however, has a good response to treatment. DLBCL is a very heterogeneous group of B-cell lymphomas. Immunohistochemistry was the 1st technique to identify surrogate markers for the molecular classification in DLBCL. MicroRNAs are transcribed by RNA polymerase II in the nucleus; they are then processed and transferred to the cytoplasm, where they change to mature microRNAs consisting of about 18~25 nucleotides. Mature microRNAs are incorporated into the RISC complex, which binds to the target mRNA and triggers mRNA degradation and/or inhibition of translation.

Methods: In this study, several microRNA expression levels in formalin-fixed paraffin-embedded (FFPE) samples of 24 patients with DLBCL and 12 FFPE samples diagnosed as lymph node reactive as the control group were investigated by real-time RT-PCR. Normalization of the results was done in comparison with the 5s rRNA gene.

Results: Our results showed an increase in the expressions of mir-155, mir-4284, mir-3182, and mir-16-5p, while the expressions of mir-4484, mir-30c-3p, mir-451, mir-145, mir-142, and mir-21 were decreased. Additionally, our results revealed no significant difference in the expression levels of mir-125b and mir-143 between the patients and the control group.

Conclusion: Further research in larger populations as well as in other cases of lymphoma is necessary to clearly identify microRNAs that are potential biomarkers for diagnosis and prognosis.

Keywords • Diffuse large-cell lymphoma • Lymphoma • Non-Hodgkin • MicroRNA • Real-time PCR

A Retrospective Analysis of Primary Central Nervous System Lymphomas

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Abstract

Background: Primary central nervous system lymphoma (PCNSL) is a rare malignancy and accounts for 1% of all lymphoma cases. Demographic features, location of the tumor, presence of risk factors, and treatment strategy in patients with PCNSL were analyzed in a single center.

Methods: In a retrospective study, patients with PCNSL admitted to Hematology and Medical Oncology Department of Shariati Hospital (Tehran, Iran) during 2006-2016 were enrolled. A questionnaire that included demographic features, location of the tumor, presence of risk factors, and route of treatment was used for data collection. Patients with more than 20% missing data in their files were excluded from the study.

Results: A total of 9 patients with PCNSL were enrolled. The median age was 38.33 (range: 21 to 72), 44.44 % were male and 55.55 % were female. Loss of consciousness, headache, blurred vision, seizure, ataxia, speech disturbance, irrelevant speaking, and paraparesis were the manifestation of the disease. None of the patients had HIV infection or other risk factors of primary CNS lymphoma. The primary site of the tumor was frontal lobe (n=2), occipital lobe (n=2), parieto-occipital lobes (n=2), fronto-parietal lobes (n=1), and pineal gland (n=1). One patient had missing data. The first line of therapy was chemotherapy in 1.11% of patients, chemoradiation in 44.44%, and combined modality (surgery and chemoradiation) in 44.44%.

Conclusion: None of the study group had the risk factor for primary CNS lymphoma. Manifestation of the disease was very different. Most of the patients had received chemoradiation.

Keywords • Central nervous system • Lymphomas • Treatment

The Evaluation of Dysregulation of Seven MicroRNAs in Chronic Lymphocytic Leukemic Patients Serum

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Abstract

Background: MicroRNAs (miRNAs) are small single-strand non-coding RNAs that cause dysregulation in a variety of cancers. Over the past decades, numerous markers of the tumor burden have been discovered in chronic lymphocytic leukemia (CLL). Among these, the microRNAs seem to have a promising role. The development and validation of miRNAs as biomarkers should have a significant impact on improving early cancer detection and diagnosis, enhancing therapeutic success, and increasing the life expectancy of patients. The present study aimed to analyze the dysregulation of in CLL patients' serum as a non-invasive method to achieve a diagnosis biomarker for CLL patients.

Methods: Seven specific primers were used in real-time PCR technique for the detection of miRNAs dysregulation. Then, the most upregulated miRNA by sponge technique was inhibited.

Results: Among the 7 microRNAs, miR-19b had the most dysregulation (upregulation) in CLL patients. The inhibition of miR-19b by miRNA sponge technique showed increased apoptosis and cell death in cancerous lymphocyte.

Conclusion: miR-19b interferes with the process of cell death by targeting the PTEN and Bim mRNAs in cancerous lymphocyte. It is shown that the evaluation of microRNAs in serum can be a non-invasive and efficient method to diagnosis and treat CLL patients.

Keywords • Chronic lymphocytic leukemia • Serum • MicroRNA • miR-19b • Sponge

Multiple Myeloma: A Case Report

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Abstract

Multiple myeloma (MM) is a relatively uncommon malignancy of plasma cell origin that often appears to have a multicentric origin within the bone. We present a case of MM in a 30-year-old female patient, who presented with a swelling in the left mandibular molar region of 2 months' duration. Panoramic and lateral radiography showed osteolytic lesions on the skull and mandible body. The serum protein electrophoresis determined ESR at 115 mm/h, and Bence Jones protein was positive in urine. The immunohistochemical examination revealed a strong reaction for the kappa light chain in all the tumor cells. Bone marrow aspiration revealed 70% plasma cell. This report showed that MM occurs even in young patients; thus, a good knowledge of the characteristics of MM is important for the early diagnosis of the disease.

Keywords • Multiple myeloma • Plasma cell • Mandible • Osteolytic lesion

Checking the Expression of the c-myc in CML Patients Positive for t(9; 22) Translocation and APL Patients Positive for t(15; 17) Translocation

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Abstract

Background: The c-myc oncogene overexpresses in different cancers. This study on 91 blood samples shows that the mRNA c-myc level increases in chronic myeloid leukemia (CML) patients positive for t(9;22) translocation but remains constant in acute promyelocytic leukemia (APL) patients positive for t(15;17) translocation. The amplification of the c-myc oncogene has been shown in different cancers. Leukemia consists of myeloid and lymphoid, in each of which the cells are stopped at a specific level of differentiation.

Methods: We gathered a group of 37 samples positive for t(9; 22) translocation (PB) and another 37 samples that were negative (NB) for the mentioned translocation. An additional group of 9 samples positive for t(15; 17) translocation (PP) and the corresponding 8 negative samples (NP). We analyzed the expression of the c-myc by qRT-PCR and measured the data using $2^{-\Delta CT}$.

Results: We saw 21.60-fold overexpression of the c-myc in the diagnosed CML patients positive for t(9;22) in comparison to the negative ones, while there was no difference between the APL patients positive for t(15;17) and the negative ones.

Conclusion: This study revealed that in the CML patients positive for t(9;22) translocation, the c-myc oncogene amplification resulted in c-myc overexpression and finally in the promotion of uncontrolled proliferation. However, given that the mRNA c-myc level was equal in the APL patients positive for t(15; 17) translocation and the negative ones, the impact of the c-myc oncogene on the t(15;17) translocation positive patients was mostly due to the increase in its protein half-life.

Keywords • Chronic myeloid leukemia • Acute promyelocytic leukemia • c-myc proteins

The Role of Immunotherapy in Multiple Myeloma

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Abstract

Multiple myeloma, also known as plasma cell myeloma, is a B-cell malignancy of plasma cells, a type of white blood cell normally responsible for producing antibodies. It is the second most common hematologic malignancy. Multiple myeloma has improved treatment paradigms. Basic research efforts towards a better understanding of normal and missing immune surveillance in myeloma have led to the development of new strategies that need the engagement of the immune system. Many of these therapies are under clinical development and have already begun offering encouraging results. Immunotherapy is the newest approach to multiple myeloma treatment. Multiple myeloma is a highly complex disease and remains incurable; with almost all patients relapsing or becoming resistant to therapy, there is now a promising new immunotherapy.

Immunotherapy includes new treatment options (e.g. monoclonal antibodies, antibody-drug compounds, chimeric antigen receptor T cell therapy, the immune checkpoint inhibitors, antibodies and tumor vaccines) either alone or in combination with the existing lines of therapy (e.g. safety factors, proteasome inhibitors, and histone deacetylase inhibitors) to increase the host immune anti-myeloma and improve clinical response.

The present study aimed to review the role of immunotherapy in modulating the bone marrow tumor microenvironment and its role in the treatment of myeloma. Clinical efficacy and safety of recently agreed therapeutic monoclonal antibodies (daratumumab, elotuzumab) are also discussed.

Keywords • Immunotherapy • Monoclonal antibodies • Multiple myeloma

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Evaluation of CD200 Marker Variations and Their Correlations with Different Stages of Disease in CLL Patients

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Abstract

Background: Chronic lymphocytic leukemia (CLL) is the most common form of leukemia in adults. It mainly affects elderly individuals and affects men twice as often as women. CLL contains different stages, with survival ranging from months to decades from diagnosis time. As any kind of therapy contains some side effects for patients, estimating the appropriate time for initiating treatment is necessary. Staging systems provided a foundation that allowed clinicians to design therapeutic strategies for the disease. Although some methods are available for determine staging, each of them has some deficiencies. CD200 is a transmembrane protein expressed on multiple cell types (e.g., thymocytes, activated T cells, B cells, dendritic cells, and endothelial cells). It regulates antitumor immunity and overexpressed CLL.

Methods: CD200 levels were measured in CD19⁺ lymphocyte by flow cytometry in 5 volunteers and 37 CLL patients from different stages.

Results: High levels of CD200 were observed in the patient group compared with the control group. In addition, there was a significant increase in the CD200 expression in the intermediate group of patients compared with the low-risk patients and a significant increase in the CD200 level in the high-risk group compared with the intermediate-risk patients.

Conclusion: A positive correlation between the level of the CD200 expression and the clinical staging system of CLL was observed in our study. Accordingly, the measurement of CD200 may have a prognostic role in patients with CLL.

Keywords • B-lymphocytes • CD200 • Flowcytometry • Leukemia • Chronic B-lymphocytic leukemia

Diabetes Insipidus in a Case of Myelodysplastic Syndrome

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Abstract

A 65-year-old female, a known case of MDS, was admitted with polydipsia, polyuria, and marked thirst 10 days prior to admission. She had a history of transfusion-dependent anemia since one year ago and treated with danazol, vitamin B12, vitamin B6, and folic acid. Physical examination revealed fever, pallor, tachycardia, and altered level of consciousness. Further evaluation showed pancytopenia associated with marked hypernatremia (Na=175 meq/L). Blood and urine cultures were obtained, and antibiotics were started. Urine volume and osmolality were checked before and 2 hours after receiving desmopressin 10 micrograms by nasal insufflation; 50% increase in urine osmolality and a decrease in urine volume were observed. A clinical diagnosis of central DI was made and magnetic resonance imaging (MRI) study of the hypothalamo-neurohypophyseal system was performed and reported to be normal. Peripheral blood smear showed pseudo-Pelger-Huët anomaly, a few monoblasts, mild dyserythropoiesis, and severe thrombocytopenia. Bone marrow aspiration and biopsy tests were done and showed more than 50% myeloblasts. The diagnosis of myelodysplastic syndrome (MDS) transformation into acute myeloid leukemia (AML) was made.

The explanation for central DI, in this case, was leukemic infiltration of hypothalamo-neurohypophyseal system. DI is a rare complication of MDS transformation into acute myeloid leukemia.

Keywords • Myelodysplastic syndrome • Central diabetes insipidus • Hypernatremia • Acute myeloid leukemia

Oxidative Stress in Normal Hematopoietic Stem Cells and Leukemia

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Abstract

Leukemia is developed following the abnormal proliferation of immature hematopoietic cells in the blood when hematopoietic stem cells lose the ability to turn normal into mature cells at different stages of maturation and differentiation. Leukemia initiating cells are specifically dependent upon the suppression of oxidative stress in the hypoglycemic bone marrow (BM) environment to be able to start their activities. Certain amounts of ROS are required for proper cellular function, but values outside this range will result in oxidative stress (OS). Long-term overactivity of reactive oxygen species (ROS) has harmful effects on the function of cells and their vital macromolecules, including the transformation of proteins into autoantigens and increased degradation of protein/DNA, which eventually leads to the change in pathways involved in the development of cancer and several other disorders. According to metabolic disorders of cancer, the relationship between OS changes, viability of cancer cells, and their response to chemotherapeutic agents affecting this pathway is undeniable. Recently, studies have been conducted to determine the effect of herbal agents and cancer chemotherapy drugs on oxidative stress pathways. Emphasizing the role of oxidative stress on stem cells in the incidence of leukemia, this paper attempts to state and summarize this subject.

Keywords • Leukemia • Hematopoietic stem cells • Free radical • Oxidative stress

Changes in the Survival of Mesenchymal Stem Cells after Exposure to Microvesicles Derived from K562 Cells

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Abstract

Background: Microvesicles are small membrane-bound particles released by different cells including healthy and tumor types. Microvesicles can transfer their contents, proteins, and RNAs to target cells and thereby transform them. This may induce apoptosis or survival depending on cell origin and the target cell.

The present study aimed to investigate the effect of microvesicles derived from K562 cells on bone marrow mesenchymal stem cells (BM-MSCs) to seek evidence of apoptosis or cell survival.

Methods: Microvesicles were isolated from K562 cell line by ultra-centrifugation and then added to BM-MSCs. BM-MSCs without microvesicles were cultured as the control group. After 7 days, cell count, cell viability By MTT assay, and qPCR for BAX gene expression were performed.

Results: Results showed lower cell number, lower cell viability rate, and higher Bax gene expression in the leukemia group in comparison with the control group. Furthermore, the results demonstrated the apoptotic effect of microvesicles derived from K562 cells on BM-MSCs.

Conclusion: The ability of microvesicles to change cells phenotype is one of the most controversial issues today. This is crucial since healthy and leukemic cells are in connection with the bone marrow microenvironment. Microvesicles are transported in microenvironment by all normal and leukemic cells. Therefore, microvesicles derived from leukemic cells may possibly change healthy cells. In order to understand disease progression, it is better to comprehend the behavior of leukemic cells in the bone marrow, which leads to the understanding of the disease progression path, leukemic cell behavior, and their effects on healthy cells.

Keywords • Cell-derived microparticles • Apoptosis • Survival

Chimeric Antigen Receptor (CAR) T-Cell for the Treatment of Childhood Leukemia

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Abstract

Relapsed and refractory acute lymphoblastic leukemia (ALL) remains difficult to treat, with minimal improvement in outcomes seen in more than 2 decades despite advances in upfront therapy and improved survival for *de novo* ALL. Immunotherapies are treatments that boost a child's own immune system to help fight leukemia. Some types of immunotherapy have shown a great deal of promise in treating ALL. In this treatment, T-cells are removed from the child's blood and genetically altered to have specific receptors (chimeric antigen receptors, CARs) on their surface. These receptors can attach to proteins on the surface of leukemia cells. The T-cells are then multiplied and given back into the child, where they can seek out the leukemia cells and launch a precise immune attack against them.

This technique has shown very encouraging results in early clinical trials against some advanced, hard-to-treat cases of ALL. Some children have had serious side effects from this treatment, including very high fevers and dangerously low blood pressure in the days after it is given.

Complete remission rates as high as 90% have been reported in children and adults with relapsed and refractory ALL treated with CAR-modified T-cells targeting the B-cell-specific antigen CD19, although several limiting factors have been identified.

We will discuss the current landscape of CAR clinical trials, cytokine release syndrome pathophysiology and management, and remaining challenges. Our study aims to evaluate the safety, efficacy, and duration of response of CAR-redirectioned autologous T-cells in children with high-risk, relapsed leukemia.

Keywords • Chimeric antigen receptor • Childhood • Leukemia
• CAR T-cell

Autophagy Regulation and Its Role in

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Abstract

Autophagy (molecular machinery for self-eating) with a dual role (tumor suppressor and tumor promoter) is a cellular process that can reveal different responses in cancer cells. It is used for the treatment of patients resistant to chemotherapy or radiation. The dominant relationships between autophagy defects and tumor genesis include protein aggregation of P62 / SQSTM1 and misfolded proteins that are damaged mitochondria and finally lead to the production of reactive oxygen species (ROS). An increase in ROS leads to DNA damage and ultimately genomic instability. Given the relatively limited studies on the use of autophagy for cancer therapy and the importance of autophagy in the regulation of hematopoietic stem cells and leukemia, a good understanding of the role of autophagy in hematopoiesis is necessary. This review, in addition to presenting a description of the role of autophagy in various stages of hematopoiesis, including quiescent, self-renewal, and multi-potency, will highlight the dual role of autophagy in cell growth and death in leukemia. The induction and inhibition of autophagy is a criterion for improving the quality of the existing treatments.

Keywords • Autophagy • Hematopoiesis • Leukemia • DNA damage • ROS

Investigation of the Growth Inhibitory Capacity of *Bacopa monnieri* on the K-562 Cell Line

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Abstract

Background: We aimed to screen and investigate the *in-vitro* anti-tumor activities of the metanolic extract of *Bacopa Monnieri* in the K-562 cancer cell line.

Methods: We used the MTT colorimetric assay to evaluate the cytotoxic activities of *Bacopa Monnieri*. In this method, a predetermined concentration of tumor cells was first seeded in 96-well plates, treated in triplicate with different concentrations of the extracts (0.1–200 µg/mL), and incubated at 37 °C with 5% of CO₂ and 95% of humidity for 48 hours. As a negative control, DMSO (solvent) was added at a concentration equal to that in the test wells. After the incubation time, we added 10 µL of MTT (5 mg/mL) to each well and incubated the plates for an additional 4 hours at 37 °C. The supernatant was removed, and 150 µL of DMSO was added in order to dissolve the formazan crystals. We read the plates at 570 nm with a reference wavelength of 630 nm in an enzyme linked immunosorbent assay (ELISA) reader. The percentage of inhibition was measured as $(1 - [\text{optical density of test} / \text{optical density of negative control}]) \times 100$. The IC₅₀ value (the concentration of 50% cell inhibition) was calculated from the graph of the inhibition percentage against different extract concentrations.

Results: The maximum of the percentage of inhibition was achieved at a concentration of 100 and 200 µg/mL of the extract of *Bacopa Monnieri*.

Conclusion: The metanolic extract of *Bacopa Monnieri* was able to inhibit the growth of the K-562 cell line in a dose-dependent manner.

Keywords • Apoptosis • Neoplasm • K-562 cell line • MTT
• *Bacopa*

Anti-Proliferative Effect of Microvesicles Derived from Human Bone Marrow Mesenchymal Stem Cells on AML-M3 Cell

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Abstract

Background: Nowadays, one of the most prevalent forms of AML is APL-(AML-M3) that has been addressed by arsenic trioxide and/or all-trans retinoic acid (ATRA). Long exposure to ATRA not only increases chemoresistance but also leads to recurrence of the disease within 3 months. Altogether, there is a need for effective treatments to address chemoresistance in APL. Recent studies considered microvesicles as a potential therapeutic agent. Microvesicles capacity to alter the behavior of cells is one of the most controversial issues. The present study aimed to investigate the effect of microvesicles on the survival of APL cell line NB4.

Methods: Mesenchymal stem cells were cultured in a culture medium. Microvesicles were separated from the supernatant and the DLS and BCA methods were performed on microvesicles. Then, microvesicles were applied on NB4 cell to assay cell viability by trypan blue staining, MTT assay, and real-time PCR.

Results: For the first time, we have demonstrated the effect of microvesicles derived from human bone marrow mesenchymal stem cells on the proliferation and apoptosis of NB-4 cell line. It is shown that by the elevation of microvesicle doses, proliferation and cell growth are dramatically hindered and the induction of apoptosis is increased in NB4 cells. The expression of anti-apoptotic genes dramatically decreased and apoptotic genes show a significant increase.

Conclusion: The results suggest that microvesicles have the potential capacity to act as an effective therapeutic agent in the treatment of APL. However, there is a need for further studies to illustrate the mechanism of microvesicles-mediated cell death.

Keywords • Cell-derived microparticles • Mesenchymal stromal cells • Leukemia • Promyelocytic • Acute

The Effect of Mesenchymal Stem Cells on Mitochondrial DNS Copy Number of Expanded Umbilical Cord Blood CD34+ Cells

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Abstract

Background: Umbilical cord blood is a limited but rich source of hematopoietic and mesenchymal stem cells (UC-MSC). It has been used in medical treatments, as it does not have limitations related to bone marrow stem cells such as invasive access. However, umbilical cord blood has limited stem cells; hence in vitro cell expansion is conducted in this regard. CD34+ stem cell culture in the vicinity of mesenchymal stem cells increases and improves the transplanted cells. It is demonstrated that long-term and short-term hematopoietic stem cells are different in term of mitochondrial content and metabolism. Long-term hematopoietic stem cells have fewer mitochondria. The number of mitochondrial DNA (mtDNA) copies of CD34+ cells in the vicinity of UC-MSC was examined in this study.

Methods: Isolated CD34+ cells from umbilical cord blood were expanded in Stemline II serum-free medium containing TPO, SCF, Flt-3 ligand (routine expansion method) and also co-cultured on UC-MSC (MSC co-culture method). The total extracted DNA from CD34+ cells at day 7 was subjected to TaqMan real-time PCR analysis to assess mtDNA copy number.

Results: mtDNA copy number of CD34+ cells significantly increased in the routine expansion method versus MSC co-culture method (CD34+ cell prior to expansion: 214 copy per cell, expanded CD34+ cell: 517 copy per cell, expanded CD34+ cell on MSC: 388 copy per cell) ($P < 0.001$).

Conclusion: Lower mtDNA copy number of expanded CD34+ cells co-cultured on MSC indicates that the cells are mainly long-term rather than short-term stem cells.

Keywords • Copy number mt-DNA • Mesenchymal stem cells
• Hematopoietic stem cells

Investigating the Effects of Zirconium DiOxide (ZrO₂) Nanoparticles on Lipid Profile, Coagulation Factors, and some Biochemical Parameters in Adult Male Rats

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Abstract

Background: Nanoparticles (NPs) are substances that can enter the body through different pathways and can damage body cells. The present study aimed to investigate the effects of zirconium dioxide (ZrO₂) nanoparticles on lipid profile, coagulation factors, and some biochemical parameters in adult male rats.

Methods: Forty adult male Wistar rats were selected randomly and divided into 5 groups, namely control, sham (received normal saline), and zirconium dioxide nanoparticles (received 100, 200, and 400 ppm orally) groups. The nanoparticles were administered orally for 30 days. Subsequently, blood was taken from the rats in order to measure the activation of ALT and AST enzymes, the level of albumin, lipid profile, creatinine, uric acid and BUN in serum, PT, PTT, platelets count in whole blood, and the level of fibrinogen in plasma. Finally, the study data were analyzed using Duncan test with the SPSS statistical software (version 22.0).

Results: The study results showed a significant increase in the activities of ALT and AST enzymes, the level of TG, Cho, BUN, uric acid in serum, fibrinogen in plasma, a significant reduction in the concentration of HDL-C, PT, and PTT in the high-dose treated group compared to the control and sham groups ($P \leq 0.05$). No significant differences in the concentrations of the albumin, LDL-C, creatinine, and platelets were observed.

Conclusion: It seems that ZrO₂NPs overdose can damage tissues (e.g. liver) and increase ALT and AST activities, uric acid, BUN, lipid profile, and raise coagulation factors in adult male rats.

Keywords • Nanoparticle • Zirconium DiOxide • Lipid profile • Blood coagulation factors • Rats

A Dose-Dependent Function of Follicular Fluid on the Proliferation and Self-Renewability of Human-BM Mesenchymal Stem Cells

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Abstract

Background: Mesenchymal stem cells (MSCs) are multipotent adult stem cells, emerging as attractive candidates for novel cell therapeutic applications. The major challenge is that a high cell dose is needed for clinical applications and expanding these cells into large-scale good manufacturing practice (GMP)-compliant protocols.

Methods: MSCs from the human-BM were isolated and their proliferation was investigated in the presence of 0.5% and 10% human follicular fluid (FF). The phenotypes and capacity of proliferation were investigated as the indexes of self-renewability of the isolated BM-MSCs. These were defined by growth curves and PDT (population doubling times).

Results: The results showed a dose-dependent function of FF on the proliferation of human BM-MSCs. FF can promote proliferation of BM-MSC as well as FBS. From 5% to 10% of the FF can promote the proliferation of BM-MSC, especially the 5% concentration of FF promote proliferation significantly higher than others.

Conclusion: The findings of the present study provide an efficient model to study the mechanism of cell proliferation and differentiation by using FF as a human supplementation in cell culture.

Keywords • Mesenchymal stem cell • Follicular fluid • Growth rate

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Tumor Microenvironment and Immune Cells Battle Story; a New Insight into Hematological Malignancies Challenge

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Abstract

Background: Recent publications have demonstrated that blood cancers are one of the leading causes of death worldwide. In this context, tumor microenvironment is supposed to be orchestrated at angiogenesis and tumor progression, which manifest in immune cell types enriched niche. The present study aimed to focus on new insights into the dissection of this tenacious synergistic collaboration.

Methods: The present study was conducted to review published research during 2000-2016 in PubMed, Scopus, and ScienceDirect databases as well as Google Scholar search engine. Five keywords were used to screen the published articles. Initially, 105 articles were identified, out of which 60 articles fulfilled the inclusion criteria.

Results: Chronic inflammation may contribute to tumor microenvironment and the maintenance of neoplastic cells. It is corroborated that receptor-ligand interaction (VCAM-1/VLA-4, Fibronectin, CD44) and notch signaling and pro-inflammatory cytokines (TNF- α , IL-1 β , GM-CSF) provide developmental and survival signals on CD13⁺/CD33⁺ B and T leukemic cells lineage, apoptosis inhibition in acute lymphoblastic leukemia (ALL), and multiple myeloma patients, as well as immune evasion of hematopoietic stem cell abnormalities and distant metastasis in T-ALLs. On the other hand, the mutualistic feedback loop of cancer stem cells and tumor-associated macrophages with immunosuppressive M2 phenotype polarization and myeloid-derived suppressor cells inhibitory functions on anti-tumor activities of NKT cells are also of clinical implications.

Conclusion: Immunopathophysiological etiologies of resident immune cells network and tumor microenvironment, as determinant factors, encourage us to a promising combination target therapy opportunities, achieving optimal clinical outcomes, destroying drug delivery barriers, and recurrence diminution.

Keywords • Hematological disorders • Immunomodulation • Tumor microenvironment • Crosstalk • Therapeutic interventions

Apoptosis Induction and Cell Cycle Arrest by Lectin Isolated from *Urtica Dioica* Agglutinin in Human Acute Lymphoid Leukemic Cell Line

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Abstract

Background: The incidence of leukemia in adults, as well as children, has been increased worldwide. It is the deadliest cancer in Iran and its incidence is rising. Different anticancer agents from plants have been discovered and extended in many laboratories. The present study aimed to evaluate the anti-leukemia effects of lectin isolated from the rhizomes and roots of *Urtica dioica* agglutinin (UDA).

Methods: UDA was isolated from the rhizomes and roots of *Urtica dioica* by affinity chromatography on chitin. Then, the effect of UDA was studied on Jurkat cell line (human T lymphocyte). The cells were treated with different concentrations of UDA in 72 hours. Finally, the analysis of apoptosis induction was done with FITC annexin V apoptosis detection kit with PI. PI staining was used for cell cycle analysis.

Results: It was revealed that UDA induced early and late apoptosis in Jurkat cell line in 128 µg/ml and G1 cell cycle arrest was observed.

Conclusion: The results indicated that UDA could exert cytotoxicity in human lymphoblastic leukemia cells undergone increased doses. Therefore, in future studies, UDA can be considered as a leukemia therapeutic agent.

Keywords • Leukemia • Stinging nettle lectin • Apoptosis

MiR-143 Induces Apoptosis via Alteration in Expression of BCL2 Family Molecules in Jurkat Cell Line

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Abstract

Background: BCL2 family members play critical roles in the regulation of apoptosis in human cells. Additionally, microRNAs (miRNAs) are also a candidate for the regulation of apoptotic pathway expression. It has been documented that miRNA-143 (miR-143) induces apoptosis in cancer cell lines but its molecular mechanisms have yet to be defined. The present study aimed to examine the mRNA levels of BCL2 family members in Jurkat cell line following treatment with miR-143.

Methods: The miR-143, a scrambled sequence, and PBS were introduced separately to the Jurkat cell and the mRNA levels of BCL2 family members were investigated and quantitated against beta-actin and GAPDH (as housekeeping genes) using real-time PCR technique.

Results: The results indicated that the mRNA levels of BCL2 as anti-apoptotic and Bak, Bax, and Bik as pro-apoptotic transcripts were significantly increased, while mRNA levels of Bad were decreased in the miR-143 transfected Jurkat cell line when compared to the scrambled sequence or PBS-treated cells.

Conclusion: The data suggest that miR-143 can lead to apoptosis via increased expression of Bak, Bax, and Bik transcripts. It appears that miR-143 can be considered as a therapeutic target in the treatment of cancers.

Keywords • MicroRNAs • Apoptosis • Neoplasm

The study of Bisphenol A on Differentiation of Human Bone Marrow Mesenchymal Stem Cells into Adipocytes

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Abstract

Background: Anemia is common throughout the world and affects all population groups. The main causes of anemia are decreased red cell production, increased red cell destruction, and blood loss. It was demonstrated that a biased differentiation of bone marrow mesenchymal stem cells (BM-MSCs) into adipocytes leads to the reduction of hematopoiesis and causes anemia. Endocrine disruptor chemicals (EDC) are components that can interfere with the body's endocrine system and produce many adverse effects. Here we examined the effect of BPA on in vitro adipogenic differentiation of BM-MSCs.

Methods: MSCs were isolated from normal BM and cultured in an expansion media. After 24 hours, the cells were cultured in groups containing BM-MSCs in DMEM or adipogenic medium plus BPA at the environmental concentration (EC) and high concentration (HC). After 14 days, the study groups were evaluated for adipogenic differentiation by Oil red-O staining (semi-quantitative) and real-time PCR to analyze gene expression.

Results: Incubation of BM-MSCs with either EC or HC of BPA led to a significant increase in adipocyte gene expression (PPARG, LPL, and leptin receptor) and oil droplet content of adipocytes differentiated from BM-MSCs ($P \leq 0.05$).

Conclusion: BPA has an impact on the differentiation of BM-MSCs and induces adipogenesis. Hence, one can expect the suppression of bone marrow hematopoiesis.

Keywords • Anemia • Adipogenesis • Bone marrow mesenchymal stem cells (BM-MSCs) • Endocrine disruptor chemicals (EDC) • Bisphenol-A (BPA)

of Methanolic Extract from Aerial parts of Juniperus Excelsa and Vincristine on Acute Lymphoblastic Leukemia Cell Lines

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Abstract

Background: A combination of natural products and conventional chemotherapeutic drugs could increase the efficacy of anticancer treatment through their potential synergistic effects. Therefore, combination therapy could potentially decrease the side effects of chemotherapeutic drugs. *J. excelsa* extract is reported to show cytotoxic effects on various cancer cells. The current study aimed to investigate the effect of methanolic extract from aerial parts of this plant on cell death activities induced by the chemotherapeutic drugs and vincristine in acute lymphoblastic leukemia cells.

Methods: Cytotoxic activity of *J. excelsa* extract and vincristine in Nalm-6 and Reh cell lines was determined using the MTT assay and synergism was evaluated using the CompuSyn software. Apoptosis was assessed by caspase-3 activity assay and flow cytometry following annexin V and propidium iodide staining. The expression levels of some apoptosis-related genes, caspase-3, BAX, and BCL-2 were determined by real-time PCR. Statistical analysis was assessed by one-way ANOVA and post-hoc Tukey multiple comparison tests.

Results: The combined treatment of VCR and *J. excelsa* extract showed a synergistic cytotoxic effect on both Nalm-6 and Reh cells at low doses of vincristine (CI<1). *J. excelsa* extract also significantly increased VCR-induced apoptosis (P<0.001). Analysis of the expression of apoptosis-related genes indicated that CASP3 and BAX genes were upregulated, while BCL-2 gene downregulated in both cells (P<0.05).

Conclusion: The results suggested the combined use of lower VCR dose and *J. excelsa* extract promoted its effects by apoptosis induction. Such combination could potentially decrease the side effects of the drug.

Keywords • Acute lymphoblastic leukemia • Vincristine • *Juniperus excelsa* • Combination therapy • Apoptosis

The Effect of Combination Therapy using Sodium Valproate, Lithium Chloride, and Celecoxib on Angiogenesis of *Chicken* Chorioallantoic Membrane

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Abstract

Background: Angiogenesis is the formation of new blood vessels from the pre-existing vasculature. This process is involved in several pathological conditions, including growth and metastasis of soft tumors. There is an increasing effort to find an effective anti-angiogenesis drugs for cancer treatment. The present study aimed to investigate the effects of combination therapy using sodium valproate, lithium, and celecoxib, on angiogenesis of *chicken* chorioallantoic membrane (CAM) in vitro.

Methods: CAM assay, using 10-day old fertilized chicken embryos, was applied to evaluate the effects of the aforementioned drugs on angiogenesis. A small window of 1.0 cm² was made on all eggshells and the exposed CAMs were treated with 15 µl of sodium valproate (20 and 40 µg/µl), lithium chloride (40 and 160 µg/µl), and celecoxib (0.05 and 2 µg/µl) individually or in combination. Control CAMs were treated with vehicle. After the incubation of drug-treated CAMs for 3 days, the numbers of vessel branches were counted in each CAM and the data were analyzed using ANOVA followed by post-hoc Tukey tests.

Results: Based on the results, all three drugs decreased the number of branches in a dose-dependent manner. In addition, the combination of drugs (sodium valproate and lithium, sodium valproate and celecoxib, celecoxib and lithium) was more effective than when drugs were applied individually.

Conclusion: It is suggested that the combination of sodium valproate, celecoxib, and lithium chloride can be considered as an effective anti-angiogenesis therapeutic modality for cancer.

Keywords • Chicken chorioallantoic membrane • Angiogenesis
• Combination therapy • Valproate • Celecoxib • Lithium

Hematopoietic Stem Cell Transplantation in MAHAK (NGO)/ 2016 Report

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Abstract

Background: The Society to Support Children Suffering from Cancer, also known as "MAHAK", was set up in 1991 as a nongovernmental and non-profit organization. The pediatric stem cell transplantation ward was inaugurated in MAHAK Hospital (Iran, Tehran) in April, 2012.

Methods: We analyzed the outcome of 150 patients from a single institution who underwent allogeneic and autologous stem cell transplantation between 2012 and 2016. A total of 135 patients (M/F=85/65) had peripheral blood stem cells as the stem cell source, 14 patients bone marrow, and 1 patient the cord blood. Forty-five patients had acute lymphoblastic leukemia, 31 had neuroblastoma, 17 had acute myeloid leukemia, 32 had Hodgkin's disease, 4 had retinoblastoma, 2 had Ewing's sarcoma, 2 had rhabdomyosarcoma, 4 had Wilms' tumor, 1 had hepatoblastoma, 3 had aplastic anemia, 3 had hemoglobinopathy, 4 had germ cell tumor, 1 had ependymoma, and 1 had osteopetrosis. Sixty-seven patients received allogeneic hematopoietic stem cell transplantation (HSCT) and 83 patients received auto HSCT.

Results: In the allogeneic peripheral blood stem cell transplantation patients, the median time to reach an absolute neutrophil count greater than $0.5 \times 10^9/L$ was 11 days, and the median time to a platelet count greater than $20 \times 10^9 /L$ was 13 days, as opposed to 19 and 22 days in the allogeneic bone marrow patients. Acute graft versus host disease of grades II to IV was observed in 67% of the patients and chronic graft versus host disease in 59% of the patients. At present, 129 (88%) patients are alive and 21 patients died due to acute respiratory distress syndrome, veno-occlusive disease, hemorrhagic stroke, sepsis, or relapse.

Conclusion: Autologous stem cell transplantation can lead to durable remissions in children and adolescents with Hodgkin's disease and solid tumors. These results indicate that although our ward is new status, both allogeneic and autologous HSCTs are feasible with outcomes similar to those in developed countries. These preliminary data suggest that HSCTs have been used as one of the standard treatments for hematological diseases and malignancies in Iran.

Keywords • Stem cell transplantation • MAHAK • Children

Silymarin caused Inhibition of Toll-Like Receptor 8 Gene Expression and Induction of Apoptosis in p53 Mutant Ramos Cancer Cell Line

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Abstract

Background: Silymarin is a standardized mixture of flavonolignans from the medicinal plant *Silybum marianum*. It has inhibitory effects on the growth of various cancer cell lines by inducing apoptosis. Toll-like receptors (TLRs) have been proposed as a novel and potentially selective target in cancer therapy. The effect of silymarin on TLR8 expression in the Ramos cancer cell line has not been investigated. The present study aimed to examine the mechanism of silymarin-induced apoptosis in Ramos cells, with particular emphasis on its effects on TLR8 expression.

Methods: The half-maximal inhibitory concentration (IC_{50}) of silymarin on cell line was examined using the MTT viability test, and the type of cell death was detected by annexin V/PI double staining. The expression of TLR8 and the activity of caspase-3 were measured in a time-dependent manner (in the IC_{50}) by real-time (RT)-PCR and colorimetric assay, respectively.

Results: The results of MTT showed that IC_{50} of Ramos was 100 μ g/ml of the silymarin after 48 hours of treatment. Flow cytometry by annexin V/PI showed that the silymarin induced early/late apoptosis in this cell line. In addition, the caspase-3 colorimetric method showed that caspase-3 had increased in the Ramos cell line after treatment and it led to a reduction in TLR8 mRNA expression in a time-dependent manner.

Conclusion: The results suggest a novel mechanism in the anticancer activity TLR signaling after silymarin treatment in p53 mutant Ramos cancer cell line and may provide a basis for the future development of anti-activity TLRs therapies.

Keywords • Gene expression • Silymarin • Apoptosis • Proliferation

Nurses help Patients Understand the Journey of Hematopoietic Stem Cell Transplantation

Rafat Rezapour Nasrabad

Abstract

Background: In hematopoietic stem cell transplantation (HSCT) units, nursing care is different from other services. Patients undergoing HSCT need the information, support, and care coordination. This procedure can be challenging in terms of the physical, mental, emotional, and spiritual aspects. Patients, family members, and health care providers may all feel the increased stress related to the experience of transplantation. The present study aimed to determine the significant role of nursing in managing the needy HSCT patients.

Methods: A descriptive research was conducted in 2016 to identify articles focused on HSCT process. The search covered library and field studies, as well as scientific databases on the internet.

Results: Nurses play a pivotal role in reducing stress and anxiety of patients and their families. Nurses work in close collaboration with a multidisciplinary medical team and are capable of planning and coordination the required care. Prior to admission and during treatment, it is essential that the recipients of HSCT receive individualized education and emotional support that includes:

- Clarifying the plan and goal of care to patients
- Providing patients with emotional support as they endure the chronic complications of HSCT, psychological strain of prolonged illness, financial burden, and strain on the caregiver
- Determining relevant resources and online information available to patients

Conclusion: Nurses are a relational bridge between the patient and medical team. Even after a patient has recovered from HSCT, the educational role of the nurse continues. The understanding of a patient's journey can greatly affect the physical, emotional, and spiritual outcomes of HSCT survivors.

Keywords • Hematopoietic • Stem cell • Transplantation

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Differentiating Mesenchymal Stem Cells from Human Umbilical Cord Blood to Cartilage by Genes Expression of Collagen II and Aggrecan

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Abstract

Background: Mesenchymal stem cells (MSCs) comprise a rare population of multipotent progenitors capable of both supporting hematopoiesis and differentiating into at least the osteogenic, adipogenic, and chondrogenic lineages. Umbilical cord blood (UCB) has turned out to be an excellent alternative source of hematopoietic stem cell (HSCs) for clinical-scale allogeneic transplantation. The present study aimed to investigate the differentiation of mesenchymal stem cells from umbilical cord blood in cartilage repair, with the expression of collagen II and aggrecan.

Methods: UCB units from full-term deliveries were collected from the unborn placenta with the informed consent of the mothers. Seven days after cell culture, their potential of survival and the growth of mesenchymal stem cells from blood-derived, at 24 and 48 hours, were evaluated using MTT assay. Finally, 14 days after the end of the chondrogenic differentiation, gene expression analysis and chondrocyte morphology formation was performed by real-time PCR and histology analyses, respectively.

Results: The real-time PCR analysis showed a significant increase in the mesenchymal stem cell viability, proliferation, and the expression of specific genes in the cartilage.

Conclusion: It is suggested that this method can be used for the induction of chondrogenic. UCB is regarded as an additional stem cell source for the repair of articular cartilage defects.

Keywords • Mesenchymal stem cells • Umbilical cord blood • Collagen 2 • Aggrecan

The Effect of Glucose on the Expression of miR-29c-3p in Mesenchymal Stem Cells

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Abstract

Background: Mesenchymal stem cells are multipotent cells, which are attractive to treat various diseases including diabetes complications. miRNAs are small and non-coding (18-21 nucleotides) molecules that contribute to different pathological and physiological processes including diabetes complications and the proliferation and differentiation of mesenchymal stem cells. miR-29c-3p target genes are associated with various tissue regeneration processes and it seems that hyper-glycemic in diabetic patients can be effective on the expression of miR-29c-3p in mesenchymal stem cells and their ability for tissue regeneration. The present study aimed to evaluate the effect of different glucose concentrations on the expression of miR-29c-3p in mesenchymal stem cells.

Methods: RNA extracted from umbilical cord mesenchymal stem cells was cultured in different glucose concentrations for 72 hours and the expression level of miR-29c-3p was measured using real-time PCR technique.

Results: The expression level of miR-29c-3p in diabetes mild and chronic was reduced compared to normal conditions.

Conclusion: miR-29c-3p requires different cellular processes involved in tissue regeneration. Increased expression of miR-29c-3p can increase apoptosis and reduce proliferation, differentiation, and angiogenesis. Based on the results, decreased expression of miR-29c-3p in umbilical cord mesenchymal stem cells, in chronic and mild diabetic conditions than normal conditions, can increase the ability of endogenous mesenchymal stem cells at the tissue damage area. In addition, it can increase the ability of umbilical cord mesenchymal stem cells, as an exogenous resource, for tissue regeneration in patients with diabetes.

Keywords • Mesenchymal stem cells • miR-29c-3p • Diabetes
• Glucose

Targeting Long Non-Coding RNAs to Enhance Therapy Efficiency and Overcome Multidrug Resistance in Hematological Malignancies

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Abstract

Systematic chemotherapy has been used as the first-line therapy for patients with hematological malignancies. Despite the remarkable achievements in anti-cancer drug development, multidrug resistance (MDR) has been a great challenge towards the successful treatment of leukemia. Recent studies have shown the involvement of long non-coding RNAs (lncRNAs) in leukemia progression and MDR mechanisms through the modulation of proteins in membrane transporters, cell cycle, drug targets, and survival or apoptosis signaling. lncRNAs have more than 200 nucleotides, influencing a great variety of functional mechanisms. Researchers have demonstrated dysregulation of lncRNAs in leukemic cells, including AML, CML, ALL, and CLL with interference of cytotoxic agents. One controversial involvement of lncRNAs is the regulation of NEAT1 in patient cells and leukemic cell lines (K562, THP-1, HL-60, Jurkat) through MDR-inducing agents, which target ABCG2 and P-gp transporters. Although lncRNAs have caught the attention of many researchers in recent decades, the true nature of their mechanisms has remained unknown. The present study aimed to investigate lncRNAs, as the key target in hematologic malignancies and drug efficiency, since they are effective factors in the advent of multidrug resistance through ABC transporters. The findings would provide a guideline on these non-coding RNAs in future studies as a novel promising target in the treatment of leukemia.

Keywords • Leukemia • Long noncoding RNA • Multidrug resistance

Aging and Stem Cell Therapy: AMPK for Rejuvenation of Aged Stem Cells and Higher Efficacy in Stem Cell Therapy

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Abstract

In recent years, tissue regeneration has become a promising field for developing stem-cell-based transplantation therapies for human patients. Adult stem cells are affected by the same aging mechanisms that involve somatic cells. One of the mechanisms that are involved in cellular aging is hyperactivation of mechanistic target of rapamycin complex 1 (mTORC1) and disruption of 5' adenosine monophosphate-activated protein kinase (AMPK). Aging of stem cells results in impaired regenerative capacity and the depletion of stem cell pools in adult tissue. In turn, this results in a lower efficacy of stem cell therapy. By utilizing effective therapeutic intervention for aged stem cells, stem cell therapy can become more promising for future application. mTORC1 inhibition is a practical approach to preserve the stem cell pool. Hence, the present study aimed to review the dynamic interaction between SIRT1, AMPK, and mTORC1. We propose that AMPK activators, such as AICAR, A769662, metformin, and NAD⁺ are practical ways to achieve optimal results in stem-cell-based transplantation therapies.

Keywords • Aging • Cell therapy • AMPK • mTORC1 • Rejuvenation