

Cover Figure

Peripheral blood smear from a patient with chronic myelomonocytic leukemia. This illustration is taken from the perspective article by Reiter and co-workers on page 1634.

Editorials and Perspectives

- 1631 Serum hepcidin: a novel diagnostic tool in disorders of iron metabolism**
Gaetano Bergamaschi and Laura Villani

During the last few years new methods for the measurement of hepcidin concentration have been developed. In this perspective article, Drs. Bergamaschi and Villani examine the potential clinical usefulness of serum hepcidin determination. See related paper on page 1748.

- 1634 Molecular basis of myelodysplastic/myeloproliferative neoplasms**
Andreas Reiter, Rosangela Invernizzi, Nicholas C.P. Cross, and Mario Cazzola

The World Health Organization classification of tumors of hematopoietic and lymphoid tissues includes within myeloid neoplasms the category myelodysplastic/myeloproliferative neoplasms. In this perspective article Drs. Reiter, Invernizzi, Cross and Cazzola discuss our present knowledge of the molecular basis of these disorders. See related paper on page 1676.

- 1639 New flow cytometry in hematological malignancies**
Jan Cools and Peter Vandenberghe

The complex and heterogeneous biology of acute lymphoblastic leukemia is unfolding as more experimental approaches such as expression profiling, DNA sequencing, and high resolution genomic arrays continue to unveil new recurrent alterations. In this perspective article, Drs. Cools and Vandenberghe examine new diagnostic applications of flow cytometry. See related paper on page 1767.

- 1641 The significance of monoclonal gammopathy of undetermined significance**
Robert A. Kyle and Shaji Kumar

Since it is now well established that all patients with multiple myeloma have a preceding monoclonal gammopathy of undetermined significance (MGUS), identification of potential risk factors for the progression becomes most important. In this perspective article, Drs. Kyle and Kumar highlight the need for a better understanding of the etiology and biology of MGUS. See related paper on page 1714.

- 1644 Granulocyte transfusion therapy: randomization after all?**
Agata Drewniak and Taco W. Kuijpers

Granulocyte transfusions were first used to treat infections in neutropenic patients in the early 1960s. The first donors were patients with chronic myeloid leukemia. Forty years later the value of these transfusions remains unclear. In this perspective article Drs. Drewniak and Kuijpers discuss the relevant data. See related paper on page 1661.

Original Articles

- 1649 Hematopoietic Stem Cells**
Generation of mesenchymal stromal cells in the presence of platelet lysate: a phenotypic and functional comparison of umbilical cord blood- and bone marrow-derived progenitors
Maria Antonietta Avanzini, Maria Ester Bernardo, Angela Maria Cometa, Cesare Perotti, Nadia Zaffaroni, Francesca Novara, Livia Visai, Antonia Moretta, Claudia Del Fante, Raffaella Villa, Lynne M. Ball, Willem E. Fibbe, Rita Maccario, and Franco Locatelli

Umbilical cord blood is an attractive source of stem cells for several cell-based therapies. In this paper, it is shown that umbilical cord blood-derived mesenchymal stroma cells, cultured in the presence of platelet lysate, have an increased proliferative potential but comparable immunomodulatory functions relative to their bone marrow-derived counterparts.

- 1661 Aplastic Anemia**
Granulocyte transfusions in severe aplastic anemia: an eleven-year experience
Karen Quillen, Edward Wong, Phillip Scheinberg, Neal S. Young, Thomas J. Walsh, Colin O. Wu, and Susan F. Leitman

Although they have been used for over 40 years, the value of granulocyte transfusions is controversial. This paper reviews outcomes in patients with severe aplastic anemia given such transfusions at the NIH. See related perspective article on page 1644.

- 1669 Chronic Myeloid Leukemia**
High rates of durable response are achieved with imatinib after treatment with interferon α plus cytarabine: results from the International Randomized Study of Interferon and STI571 (IRIS) trial
François Guilhot, Brian Druker, Richard A. Larson, Insa Gathmann, Charlene So, Roger Waltzman, and Stephen G. O'Brien

Imatinib is the standard of care for patients with newly diagnosed chronic-phase chronic myeloid leukemia. This is the largest analysis to date describing the efficacy of imatinib in patients who have received prior therapies for chronic myeloid leukemia and it demonstrates excellent responses to imatinib in this context.

1676 Myelodysplastic/Myeloproliferative Neoplasms
TET2 gene mutation is a frequent and adverse event in chronic myelomonocytic leukemia
 Olivier Kosmider, Véronique Gelsi-Boyer, Marion Ciudad, Cindy Racœur Valérie Jooste, Norbert Vey, Bruno Quesnel, Pierre Fenaux, Jean-Noël Bastie, Odile Beyne-Rauzy, Aspasia Stamatoulas, François Dreyfus, Norbert Ifrah, Stéphane de Botton, William Vainchenker, Oliver A. Bernard, Daniel Birnbaum, Michaëla Fontenay, and Eric Solary on behalf of the Groupe Francophone des Myélodysplasies

Acquired somatic deletions and loss-of-function mutations in one or several codons of the TET2 (Ten-Eleven Translocation-2) gene were recently identified in hematopoietic cells from patients with myeloid neoplasms. This study shows that TET2 mutations are more frequent in chronic myelomonocytic leukemia than in other subgroups of myeloid neoplasms studied so far.

1682 Pediatric Leukemias
Clinical characteristics and outcome of children with biphenotypic acute leukemia
 Amal S. Al-Seraihy, Tarek M. Owaidah, Mouhab Ayas, Hassan El-Solh, Mohammed Al-Mahr, Ali Al-Ahmari, and Asim F. Belgaumi

This study from Saudi Arabia found that 4% of 633 cases of pediatric acute leukemia were biphenotypic. The authors describe the clinical features of these patients and their response to treatment including stem cell transplantation.

1691 Malignant Lymphomas
Sperm quality before treatment in patients with early stage Hodgkin's lymphoma enrolled in EORTC-GELA Lymphoma Group trials
 Marleen A.E. van der Kaaij, Natacha Heutte, Jannie van Echten-Arends, John M.M. Raemaekers, Patrice Carde, Evert M. Noordijk, Christophe Fermé, José Thomas, Houchingue Eghbali, Pauline Brice, Caroline Bonmati, Michel Henry-Amar, and Hanneke C. Kluijn-Nelemans

Although widely recommended, cryopreservation of sperm is sometimes not performed for patients with Hodgkin's lymphoma because of presumed poor sperm quality related to the disease. In this large study of males with Hodgkin's lymphoma, 90% had good or intermediate sperm quality, indicating that in most patients with early-stage Hodgkin's lymphoma sperm quality before treatment is good enough for future fatherhood.

1698 Chronic Lymphocytic Leukemia
Akt inhibitors induce apoptosis in chronic lymphocytic leukemia cells
 Mercè de Frias, Daniel Iglesias-Serret, Ana M. Cosiáls, Llorenç Coll-Mulet, Antonio F. Santidrián, Diana M. González-Gironès, Esmeralda de la Banda, Gabriel Pons, and Joan Gil

Chronic lymphocytic leukemia (CLL) is now divisible into

subsets with distinct clinical behaviors. The biology underlying these differences appears to include signaling pathways through the B-cell receptor and other receptors. The phosphatidylinositol-3-kinase/Akt pathway is important, raising the possibility that inhibitors could have therapeutic potential. Encouragingly, two inhibitors were found to induce preferential apoptosis of CLL cells, irrespective of TP53 status, with increases in NOXA and PUMA protein levels and a decrease in MCL-1.

1708 Monoclonal Gammopathies
Timing of acquisition of deletion 13 in plasma cell dyscrasias is dependent on genetic context
 Laura Chiecchio, Gian Paolo Dagrada, Ashraf H. Ibrahim, Elizabet Dachs Cabanas, Rebecca K.M. Protheroe, David M. Stockley, Kim H. Orchard, Nicholas C.P. Cross, Christine J. Harrison, and Fiona M. Ross, on behalf of the UK Myeloma Forum

Monoclonal gammopathy of undetermined significance (MGUS) and smoldering myeloma (SMM) are characterized by an expansion of monoclonal plasma cells and can progress to symptomatic multiple myeloma. This study assessed the incidence and the association of monosomy 13 with IgH translocations, ploidy status and deletions of 16q23 and TP53 in a large series of MGUS and SMM patients.

1714 Monoclonal Gammopathies
Patterns of survival and causes of death following a diagnosis of monoclonal gammopathy of undetermined significance: a population-based study
 Sigurdur Y. Kristinsson, Magnus Björkholm, Therese M-L Andersson, Sandra Eforanta, Paul W. Dickman, Lynn R. Goldin, Cecilie Blimark, Ulf-Henrik Mellqvist, Anders Wahlin, Ingemar Turesson, and Ola Landgren

There are limited data on survival patterns among patients with monoclonal gammopathy of undetermined significance (MGUS). In a study of 4,259 MGUS patients, the authors found that individuals diagnosed with MGUS in a clinical setting had a significantly reduced life expectancy. See related perspective article on page 1641.

1721 Blood Coagulation
Species-specific anticoagulant and mitogenic activities of murine protein S
 José A. Fernández, Mary J. Heeb, Xiao Xu, Itender Singh, Berislav V. Zlokovic, and John H. Griffin

Mice and other animals have proved extremely useful testing grounds for hypotheses and for potential therapies. However, significant interspecies differences can confound correct interpretation and attempts to extrapolate results to man. In this study Fernandez and co-workers demonstrate that the human and murine protein C-protein S systems function in a similar way but do not interact efficiently with one another.

Decision Making & Problem Solving

- 1732 **Aplastic anemia**
Unrelated donor stem cell transplantation in acquired severe aplastic anemia: a systematic review
Frank Peinemann, Ulrich Grouven, Nicolaus Kröger, Max Pittler, Beate Zschorlich, and Stefan Lange

Acquired severe aplastic anemia is a rare disease characterized by an immune-mediated functional impairment of hematopoietic stem cells. Transplantation of these cells from unrelated donors is a treatment option frequently offered to patients after failed immunosuppressive therapy. This systematic review indicates that unrelated donor hematopoietic stem cell transplantation in patients with acquired severe aplastic anemia after failure of immunosuppressive therapy is a valid treatment option.

Brief Reports

- 1743 **Bone Marrow Failure**
Changes in cytokine profile pre- and post-immunosuppression in acquired aplastic anemia
Carlo Dufour, Elisa Ferretti, Francesca Bagnasco, Oriana Burlando, Marina Lanciotti, Ugo Ramenghi, Paola Saracco, Maria Teresa Van Lint, Daniela Longoni, Giovanni Fernando Torelli, Marta Pillon, Anna Locasciulli, Aldo Misuraca, Milena La Spina, Andrea Bacigalupo, Vito Pistoia, Anna Corcione, and Johanna Svahn on behalf of the Marrow Failure Study Group of the AIEOP
- Some patients with aplastic anemia respond to immunosuppressive therapy. Here the authors compare pre and post-immunosuppressive therapy levels of CD3/interferon- γ secreting cells in responders and non-responders.

- 1748 **Disorders of Iron Metabolism**
Results of the first international round robin for the quantification of urinary and plasma hepcidin assays: need for standardization
Joyce J.C. Kroot, Erwin H.J.M. Kemna, Sukhvinder S. Bansal, Mark Busbridge, Natascia Campostrini, Domenico Girelli, Robert C. Hider, Vasiliki Koliarakis, Avgi Mamalaki, Gordana Olbina, Naohisa Tomosugi, Chris Tselepis, Douglas G. Ward, Tomas Ganz, Jan C.M. Hendriks, and Dorine W. Swinkels

This study indicates that hepcidin levels reported by various methods vary considerably but analytical variance is generally low and similar for all methods. See related perspective article on page 1631.

- 1753 **Red Cell Disorders**
 β -spectrin^{Bari}: a truncated β -chain responsible for dominant hereditary spherocytosis
Silverio Perrotta, Fulvio Della Ragione, Francesca Rossi, Rosa Anna Avvisati, Daniela Di Pinto, Giovanna De Mieri, Saverio Scianguetta, Silvia Mancusi, Luigia De Falco, Vito Marano, and Achille Iolascon

This report describes a β -spectrin variant, named β -spectrin^{Bari}, characterized by a truncated chain and associated with hereditary spherocytosis.

- 1758 **Chronic Myeloid Leukemia**
Pancreatic enzyme elevation in chronic myeloid leukemia patients treated with nilotinib after imatinib failure
Francesca Palandri, Fausto Castagnetti, Simona Soverini, Angela Poerio, Gabriele Gugliotta, Simona Luatti, Marilina Amabile, Giovanni Martinelli, Gianantonio Rosti, and Michele Baccarani

An increase in the serum concentration of pancreatic enzymes (amylase and lipase) was reported in a proportion of imatinib-resistant and/or intolerant Philadelphia-positive chronic myeloid leukemia patients treated with nilotinib. This report describes chronic myeloid leukemia patients who developed serum lipase/amylase elevation during treatment with nilotinib.

- 1762 **Myelodysplastic Syndromes**
Clonal heterogeneity in the 5q- syndrome: p53 expressing progenitors prevail during lenalidomide treatment and expand at disease progression
Martin Jädersten, Leonie Saft, Andrea Pellagatti, Gudrun Göhring, James S. Wainscoat, Jacqueline Boulthwood, Anna Porwit, Brigitte Schlegelberger, and Eva Hellström-Lindberg

Transformation to acute myeloid leukemia may occur in patients with myelodysplastic syndrome with isolated del(5q) treated with lenalidomide, particularly in those without a cytogenetic response. In this study, the authors performed molecular investigations in a patient with classical 5q- syndrome with complete erythroid and partial cytogenetic response to lenalidomide, who later developed high-risk myelodysplastic syndrome with a complex karyotype.

- 1767 **Acute lymphoblastic leukemia**
An accurate and rapid flow cytometric diagnosis of BCR/ABL positive acute lymphoblastic leukemia
Sara Raponi, Maria Stefania De Propriis, Hobert Wai, Stefania Intoppa, Loredana Elia, Daniela Diverio, Antonella Vitale, Robin Foà, and Anna Guarini

This report describes an accurate and rapid flow cytometric diagnosis of BCR/ABL positive acute lymphoblastic leukemia. See related perspective article on page 1639.

- 1771 **Gaucher Disease**
Real-world clinical experience with long-term miglustat maintenance therapy in type 1 Gaucher disease: the ZAGAL project
Pilar Giraldo, Pilar Alfonso, Koldo Atutxa, María A. Fernández-Galán, Abelardo Barez, Rafael Franco, Dora Alonso, Alejandro Martín, Paz Latre, and Miguel Pocovi
- There are few published data from real-world clinical experience with miglustat, an oral inhibitor of glucosylceramide synthase, in type 1 Gaucher disease. This study suggests that miglustat is an effective therapy for the long-term maintenance of patients with type 1 Gaucher disease previously stabilized with enzyme replacement therapy.*

Letters to the Editor

- 1776 **Iron Overload**
Early cardiac iron overload in children with transfusion-dependent anemias
Juliano Lara Fernandes, Antonio Fabron Jr, and Monica Verissimo
- 1777 **Thalassemia Syndromes**
Improved survival in thalassemia major patients on switching from desferrioxamine to combined chelation therapy with desferrioxamine and deferiprone
Paul T. Telfer, Fiona Warburton, Soteroula Christou, Michael Hadjigavriel, Maria Sitarou, Anita Kolnagou, and Michael Angeliniotis
- 1778 **Acute Leukemia**
What is the optimal treatment for biphenotypic acute leukemia?
Changcheng Zheng, Jingsheng Wu, Xin Liu, Kaiyang Ding, Xiaoyan Cai, and Weibo Zhu

- 1780 **Acute Leukemia**
What is the optimal treatment for biphenotypic acute leukemia? Authors' reply
Jianmin Wang, and Xiaoqian Xu

- 1781 **Malignant Lymphomas**
The targeting of the sole cyclin D1 is not adequate for mantle cell lymphoma and myeloma therapies
Guergana Tchakarska, Anne Le Lan-Leguen, Lucile Roth, and Brigitte Sola

- 1783 **Platelets**
The GPIIb/IIIa antagonist drugs eptifibatid and tirofiban do not induce activation of apoptosis executioner caspase-3 in resting platelets but inhibit caspase-3 activation in platelets stimulated with thrombin or calcium ionophore A23187
Valery Leytin, Asuman Mutlu, Sergiy Mykhaylov, David J. Allen, Armen V. Gyulkhandanyan, and John Freedman

Continuing Medical Education

Biphenotypic acute leukemia in children

The implications of a diagnosis of monoclonal gammopathy of undetermined significance

TET2 gene mutations in chronic myelomonocytic leukemia

Granulocyte transfusions in severe aplastic anemia