

Cover Figure

FOXP3⁺ regulatory T cells in Hodgkin's lymphoma.
This illustration is taken from the article by Tzankov
et al. on page 193.

Editorials and Perspectives

- 161 **Monitoring treatment of chronic myeloid leukemia**
Michele Baccarani, Fabrizio Pane,
and Giuseppe Saglio
- Monitoring treatment of chronic myeloid leukemia is not only important for ensuring that a patient is receiving the best treatment, but is also convenient from a pharmaco-economic point of view. See related papers on pages 178 and 186.*
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- 169 **Childhood polycythemia vera and essential thrombocythemia: does their pathogenesis overlap with that of adult patients?**
Luciana Teofili, Robin Foà, Fiorina Giona,
and Luigi Maria Larocca
- Pediatric erythrocytosis and thrombocytosis are heterogeneous diseases, including both sporadic and hereditary disorders. A specific diagnostic approach for these conditions is proposed.*
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- 172 **Acquired thrombotic thrombocytopenic purpura: ADAMTS13 activity, anti-ADAMTS13 autoantibodies and risk of recurrent disease**
Bernhard Lämmle, Johanna A. Kremer Hovinga,
and James N. George
- Our understanding of the pathophysiology of acquired thrombotic thrombocytopenic purpura has improved remarkably over the past ten years. Nonetheless, recent studies raise new questions concerning ADAMTS13 activity, anti-ADAMTS13 autoantibodies and risk of recurrent disease. These questions likely far outweigh the substantial knowledge gained. See related article on page 232.*

Original Articles

- 178 **Chronic Myeloid Leukemia**
Comparison of bone marrow high mitotic index metaphase fluorescence *in situ* hybridization to peripheral blood and bone marrow real time quantitative polymerase chain reaction on the International Scale for detecting residual disease in chronic myeloid leukemia
Tuija Lundán, Vesa Juvonen, Martin C. Mueller,
Satu Mustjoki, Taina Lakkala, Veli Kairisto,
Andreas Hochhaus, Sakari Knuutila,
and Kimmo Porkka
- Real time quantitative polymerase chain reaction analyses allow reliable determination of minimal residual disease in*

chronic myeloid leukemia. Peripheral blood is the first choice as a source of sample for this analysis, and the International Scale for standardization and reporting of minimal residual disease results should be used.

- 186 **Chronic Myeloid Leukemia**
Dynamics of BCR-ABL mutated clones prior to hematologic or cytogenetic resistance to imatinib
Thomas Ernst, Philipp Erben, Martin C. Müller,
Peter Paschka, Thomas Schenk, Jana Hoffmann,
Sebastian Kreil, Paul La Rosée, Rüdiger Hehlmann,
and Andreas Hochhaus
- Mutations of the BCR-ABL tyrosine domain represent a major cause of resistance to tyrosine kinase inhibitors in chronic myeloid leukemia. The appearance of BCR-ABL mutations during imatinib therapy likely indicates imminent relapse, and their early detection might allow reconsideration of the therapeutic strategy.*
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- 193 **Malignant Lymphomas**
Correlation of high numbers of intratumoral FOXP3⁺ regulatory T cells with improved survival in germinal center-like diffuse large B-cell lymphoma, follicular lymphoma and classical Hodgkin's lymphoma
Alexandar Tzankov, Cecile Meier, Petra Hirschmann,
Philip Went, Stefano A. Pileri, and Stephan Dirnhöfer
- FOXP3⁺ regulatory T-cells represent important modulators of lymphoma/host microenvironment. Their number may represent a positive prognostic factor in patients with germinal center-like diffuse large B-cell lymphoma, follicular lymphoma, and classical Hodgkin's lymphoma.*
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- 201 **Malignant Lymphomas**
Dissemination patterns in non-gastric MALT lymphoma
Jan Paul de Boer, Reimier Frederik Hiddink,
Markus Raderer, Ninja Antonini, Berthe Mauricia
Pauline Aleman, Henk Boot, and Daphne de Jong
- Primary extranodal non-gastric marginal zone MALT lymphoma frequently present with stage IV disease and multifocal disease, and a site-specific dissemination pattern. Extensive staging at diagnosis of fundamental importance.*
-
- 207 **Malignant Lymphomas**
High clinical and molecular response rates with fludarabine, cyclophosphamide and mitoxantrone in previously untreated patients with advanced stage follicular lymphoma
Silvia Montoto, Carol Moreno, Eva Domingo-Doménech, Cristina Estany, Albert Oriol, Albert Altés,
Joan Besalduch, Carme Pedro, Santiago Gardella,
Lourdes Escoda, Antoni Asensio, Pilar Vivancos, Pilar Galán, Alberto Fernández de Sevilla, Josep M. Ribera,
Javier Briones, Dolores Colomer, Elias Campo, Emili Montserrat, and Armando López-Guillermo for the Grup per l'Estudi dels Limfomes de Catalunya I Balears (GELCAB), Spain
- Combination chemotherapy with fludarabine, cyclophosphamide and mitoxantrone results in high complete and*

molecular response rates with prolonged response duration in previously untreated patients with advanced stage follicular lymphoma.

- 215 **Chronic Lymphocytic Leukemia**
Multicenter study of ZAP-70 expression in patients with B-cell chronic lymphocytic leukemia using an optimized flow cytometry method

Nathalie Gachard, Aurélie Salviat, Catherine Boutet, Christine Arnoulet, Françoise Durrieu, Bernard Lenormand, Stéphane Leprêtre, Sylviane Olschwang, Fabrice Jardin, Marina Lafage-Pochitaloff, Dominique Penther, Danielle Sainty, Liliane Reminieras, Jean Feuillard, and Marie Christine Béné for the GEIL

ZAP-70 expression appears to be a promising prognostic factor in B-cell chronic lymphocytic leukemia. This article describes an optimized flow cytometry method for direct detection of ZAP-70.

- 224 **Hemostasis**
Manipulating the quality control pathway in transfected cells: low temperature allows rescue of secretion-defective fibrinogen mutants

Dung Vu, Corinne Di Sanza, and Marguerite Neerman-Arbez

Congenital afibrinogenemia is caused by mutations in one of the three fibrinogen-encoding genes, secretion-defective fibrinogen mutants are retained in a pre-Golgi compartment in hepatocytes. This study shows that lowering the incubation temperature can restore the secretion of mutant fibrinogen molecules in transfected COS-7 cells.

- 232 **Thrombosis**
ADAMTS13 and anti-ADAMTS13 antibodies as markers for recurrence of acquired thrombotic thrombocytopenic purpura during remission

Flora Peyvandi, Silvia Lavoretano, Roberta Palla, Hendrik B. Feys, Karen Vanhoorelbeke, Tullia Battaglioli, Carla Valsecchi, Maria Teresa Canciani, Fabrizio Fabris, Samo Zver, Marienn Réti, Danijela Mikovic, Mehran Karimi, Gaetano Giuffrida, Luca Laurenti, and Pier Mannuccio Mannucci

Acquired thrombotic thrombocytopenic purpura (TTP) is often due to anti-ADAMTS13 antibodies that inhibit the proteolytic activity of the plasma metallo-protease and/or accelerate its clearance. Survivors of an acute episode of TTP with severely reduced levels of ADAMTS13 and/or with anti-ADAMTS13 antibodies during remission are at high risk of developing another episode of TTP.

- 240 **Stem Cell Transplantation**
Evidence for neo-generation of T cells by the thymus after non-myceloablative conditioning

Emilie Castermans, Frédéric Baron, Evelyne Willems,

Nicole Schaaf-Lafontaine, Nathalie Meuris, André Gothot, Jean-François Vanbellighen, Christian Herens, Laurence Seidel, Vincent Geenen, Remi Cheynier, and Yves Beguin

In patients given allogeneic stem cell transplantation with non-myceloablative conditioning, immune recovery is initially driven by peripheral expansion of the graft-contained mature T cell, while T-cell neo-generation by the thymus plays an important role in long-term immune reconstitution.

- 248 **Stem Cell Transplantation**
Human cytomegalovirus-specific CD4⁺ and CD8⁺ T-cell reconstitution in adult allogeneic hematopoietic stem cell transplant recipients and immune control of viral infection

Daniele Lilleri, Chiara Fornara, Antonella Chiesa, Daniela Caldera, Emilio Paolo Alessandrino, and Giuseppe Gerna

Human cytomegalovirus infection is the most frequent viral complication in patients undergoing hematopoietic stem cell transplantation. Pre-transplant human cytomegalovirus serostatus of the recipient is the main trigger for specific T-cell reconstitution.

- 257 **Stem Cell Transplantation**
Fludarabine-melphalan as a preparative regimen for reduced-intensity allogeneic stem cell transplantation in relapsed and refractory Hodgkin's lymphoma: the updated M.D. Anderson Cancer Center experience

Paolo Anderlini, Rima Saliba, Sandra Acholonu, Sergio A. Giral, Borje Andersson, Naoto T. Ueno, Chitra Hosang, Issa F. Khouri, Daniel Couriel, Marcos de Lima, Muzaffar H. Qazilbash, Barbara Pro, Jorge Romaguera, Luis Fayad, Frederick Hagemester, Anas Younes, Mark F. Munsell, and Richard E. Champlin

Allogeneic stem cell transplantation is employed in patients with relapsed and refractory Hodgkin's lymphoma. In this setting, transplant-related mortality is particularly high. Fludarabine-melphalan as a preparative regimen for reduced-intensity conditioning appears to be associated with a significant reduction in transplant-related mortality.

- 265 **Stem Cell Transplantation**
A comparison between low intensity and reduced intensity conditioning in allogeneic hematopoietic stem cell transplantation for solid tumors

Réka Conrad, Mats Remberger, Kerstin Cederlund, Olle Ringdén, and Lisbeth Barkholt

Allogeneic hematopoietic stem cell transplantation can produce a graft-versus-tumor-effect in patients with solid tumors. Adjuvant cell therapy with donor lymphocyte infusion may augment this graft-versus-tumor effect.

Decision Making and Problem Solving

- 273 **Thrombosis**
Clinical characteristics and management of cancer-associated acute venous thromboembolism: findings from the MASTER Registry
Davide Imberti, Giancarlo Agnelli, Walter Ageno, Marco Moia, Gualtiero Palareti, Riccardo Pistelli, Romina Rossi, and Melina Verso for the MASTER Investigators

MASTER is a multicenter registry of consecutively recruited patients with symptomatic, objectively confirmed, acute venous thromboembolism. One fifth of the patients enrolled had cancer. In these patients, venous thromboembolism has peculiar features, and its management is more problematic.

Brief Reports

- 279 **Erythrocytosis**
Elevated homocysteine, glutathione and cysteinylglycine concentrations in patients homozygous for the Chuvash polycythemia VHL mutation
Adelina I. Sergueeva, Galina Y. Miasnikova, Daniel J. Okhotin, Alla A. Levina, Zufan Debebe, Tatiana Ammosova, Xiaomei Niu, Elena A. Romanova, Sergei Nekhai, Patricia M. DiBello, Donald W. Jacobsen, Josef T. Prchal, and Victor R. Gordeuk

Up-regulated hypoxia sensing may influence multiple steps in thiol metabolism and result in hyperhomocysteinemia.

- 283 **Acute Myeloid Leukemia**
Cup-like acute myeloid leukemia – new disease or artificial phenomenon?
Frank P. Kroschinsky, Ulrike Schäkel, Rainer Fischer, Brigitte Mohr, Uta Oelschlaegel, Roland Repp, Markus Schaich, Silke Soucek, Gustavo Baretton, Gerhard Ehninger, and Christian Thiede on behalf of the DSIL (Deutsche Studieninitiative Leukämie) Study Group

In acute myeloid leukemia, cup-like nuclear morphology is an indicator of normal karyotype.

- 287 **Acute Lymphoblastic Leukemia**
Karyotype at diagnosis is the major prognostic factor predicting relapse-free survival for patients with Philadelphia chromosome-positive acute lymphoblastic leukemia treated with imatinib-combined chemotherapy
Masamitsu Yanada, Jin Takeuchi, Isamu Sugiura, Hideki Akiyama, Noriko Usui, Fumiharu Yagasaki, Kazuhiro Nishii, Yasunori Ueda, Makoto Takeuchi, Shuichi Miyawaki, Atsuo Maruta, Hiroto Narimatsu, Yasushi Miyazaki, Shigeki Ohtake, Itsuro Jimmai, Keitaro Matsuo, Tomoki Naoe, and Ryuzo Ohno for the Japan Adult Leukemia Study Group

In patients with Philadelphia chromosome-positive acute lymphoblastic leukemia treated with imatinib-combined chemotherapy, the presence of secondary chromosome aberrations in addition to (t9;22) at diagnosis represents an independent risk factor for relapse.

- 291 **Hemophagocytic Lymphohistiocytosis**
Hemophagocytic lymphohistiocytosis as severe adverse event of antineoplastic treatment in children
Herwig Lackner, Christian Urban, Petra Sovinz, Martin Benesch, Andrea Moser, and Wolfgang Schwinger

Hemophagocytic lymphohistiocytosis is a rare but life-threatening complication of antineoplastic therapy in children. Early diagnosis is of fundamental importance.

- 295 **Amyloidosis**
Efficacy of bortezomib in systemic AL amyloidosis with relapsed/refractory clonal disease
Ashutosh D. Wechalekar, Helen J. Lachmann, Mark Offer, Philip N. Hawkins, Julian D. Gillmore

Bortezomib may be effective in patients with AL amyloidosis with relapsed/refractory disease.

- 299 **Disorders of Hemostasis**
Factor X^{Debreccen}: Gly204Arg mutation in factor X causes the synthesis of a non-secretable protein and severe factor X deficiency
Zsuzsanna Bereczky, Helga Bárdos, István Komáromi, Csongor Kiss, Gizella Haramura, Eva Afzner, Róza Adány, and László Muszbek

Inherited factor X deficiency is a rare coagulopathy with severe bleeding symptoms in homozygous patients. Several mutations in the F10 gene have been described, the Gly204Arg mutation causes structural changes in the molecule and a secretion defect due to retention at the trans Golgi-late endosome level.

- 303 **Stem Cell Transplantation**
Reduced intensity conditioning allogeneic stem cell transplantation for adult patients with acute lymphoblastic leukemia: a retrospective study from the European Group for Blood and Marrow Transplantation
Mohamad Mohty, Myriam Labopin, Reza Tabrizzi, Niklas Theorin, Axel A Fauser, Alessandro Rambaldi, Johan Maertens, Shimon Slavin, Ignazio Majolino, Arnon Nagler, Didier Blaise, and Vanderson Rocha on behalf of the Acute Leukemia Working Party

Reduced intensity conditioning allogeneic stem cell transplantation may be a feasible therapeutic option for adult patients with acute lymphoblastic leukemia.

Letters to the Editor

- 307 **Sickle Cell Disease**
Sickle cell patients are characterized by a reduced glycoalyx volume
Eduard J. van Beers, Max Nieuwdorp, Ashley J. Duits, Ludo M.Evers, John-John B. Schmog, and Bart J.Biemond on behalf of the CURAMA Study Group
- 309 **Disorders of Iron Metabolism**
New *TFR2* mutations in young Italian patients with hemochromatosis
Giorgio Biasiotto, Clara Camaschella, Gian Luca Forni, Anna Polotti, Gabriella Zecchina, and Paolo Arosio
- 311 **Thalassemia Syndromes**
Atrial dysfunction as a marker of iron cardiotoxicity in thalassemia major
Walter Li, Thomas Coates, and John C. Wood
- 313 **Erythropoietin**
Recombinant erythropoietin found in seized blood bags from sportsmen
Joaquim Mallorquí, Jordi Segura, Carme de Bolòs, Ricardo Gutiérrez-Gallego, and José A. Pascual
- 315 **Myelodysplastic Syndromes**
Unusual clonal evolution involving 5q in a case of myelodysplastic syndrome with deletion 5q 31 treated with lenalidomide
Virginie Eclache, Anna Da Rocha, Genevieve Le Roux, and Pierre Fenaux
- 317 **Chronic Myeloid Leukemia**
Alterations in creatine kinase, phosphate and lipid values in patients with chronic myeloid leukemia during treatment with imatinib
Anna Franceschino, Lucia Tornaghi, Valerie Benemacher, Sarit Assouline, and Carlo Gambacorti-Passerini
- 319 **Malignant Lymphomas**
Rare occurrence of *IgVH* gene translocations and restricted *IgVH* gene repertoire in ocular MALT-type lymphoma
Patrick Adam, Eugenia Haralambieva, Martina Hartmann, Zhengrong Mao, German Ott, and Andreas Rosenwald

Online Only Articles

- e24 **Reply. Pereira A. Cryoprecipitate versus commercial fibrinogen concentrate in patients who occasionally require a therapeutic supply of fibrinogen: risk comparison in the case of an emerging transfusion-transmitted infection.**
Haematologica 2007;92:846-9.
A. Gröner
- e27 **Reply. Gröner A. [Pereira A. Cryoprecipitate versus commercial fibrinogen concentrate in patients who occasionally require a therapeutic supply of fibrinogen: risk comparison in the case of an emerging transfusion-transmitted infection.**
Haematologica 2007; 92:846-9].
A. Pereira
- e28 **Central nervous system relapse occurs in about 5% of cases of acute promyelocytic leukaemia**
C. Castagnola, C. Elena, M. Merli
- e29 **Mediterranean macrothrombocytopenia and phytosterolaemia/sitosterolaemia**
G.W. Stewart, M. Makris
- e30 **Characteristics and stage of the underlying diseases could determine the risk of opportunistic infections in patients receiving alemtuzumab**
A. Nosari, A. Tedeschi, F. Ricci, M. Montillo