Belgian Journal of Hematology

The Belgian Journal of Hematology is the official journal of the Belgian Hematological Society (BHS), the Belgian Society on Thrombosis and Haemostasis (BSTH), the Belgian Society of Paediatric Haematology and Oncology (BSPHO) and the Belgian Society for Analytical Cytology (BVAC-ABCA)

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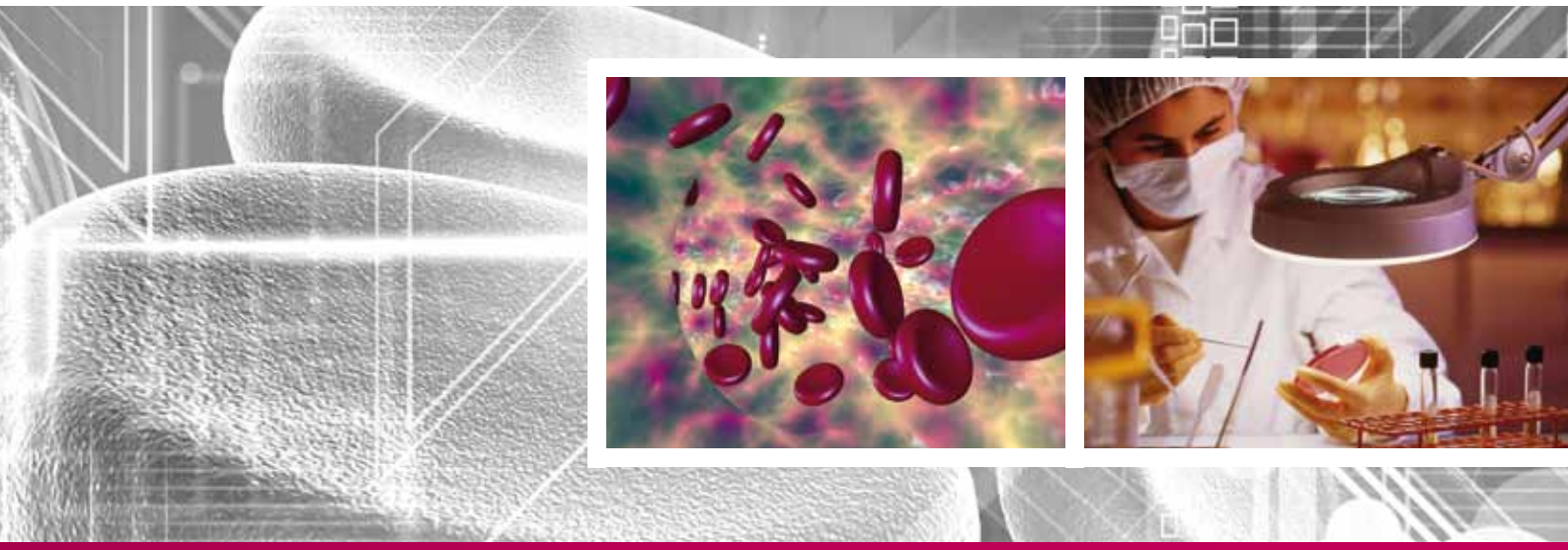

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colophon

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De BJH aims to be a peer-reviewedhematology journal covering all aspects of the diagnostic and clinical management of hematology patients, reflecting a multidisciplinary approach to therapy. It aims informing clinicians active in the field of hematology in Belgium and Luxembourg, thereby giving clinicians a solid support for daily practice. The BJH targets al specialists and specialists in training with an active interest and participation in the clinical management and treatment of hematological diseases. The BJH is distributed for free via controlled circulation amongst all medical specialists working as clinicians in the field of Hematology in Belgium and Luxembourg. This includes fields as hemostasis and thrombosis, but also transfusion medicine and transplantation medicine. The BJH is also sent to clinical chemistry specialists, doctors working in transfusion departments and doctors performing research in the field of hematology, as well as to all specialists in training within these fields in Belgium and Luxembourg.

The content is determined by an independent Editorial Board, consisting of key opinion leaders within the field of hematology, to ensure that articles published in the BJH are truly objective and independent. The journal welcomes contributions from readers, however these will be evaluated for publication by reviewers from the Editorial Board or, occasionally, from outside the Board. For more information, please turn to the publisher, Ariez International.

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Ariez International B.V.
Ms. E. van Zanten, MSc
c/o Oude Houtlei 118-120
9000 Gent, Belgium
Tel: 0031 75 642 94 20
Fax: 0031 75 642 94 21
E-mail: editor@bjh.be

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Volume 3, Issue 1, March 2012

Introduction

Dear reader,

Not only do we have a new prime-minister since the last edition of this journal, but the Belgian Hematological Society also held it much appreciated annual meeting in Liège, at the end of last January. You'll find the abstract book of this congress with the current issue of BJH.

The journal itself contains the regular topics, with -I do hope- something for everyone's taste. We have an interesting review article on musculoskeletal manifestations in paediatric ALL, and one on how to avoid life-threatening hypokalaemia in T-ALL.

The pharmacotherapy section is devoted to clofarabine; a trial in Von Willebrand disease is presented, and the haematothesis summarises intriguing work in the evolving field of immunotherapy and dendritic cells.

Apart from the abstracts of our national society, André Bosly attended the ASH meeting of 2011, and presents his 'best of'.

We end with announcements, for which we ask your contribution; please keep sending us the agenda of events you organise in the field of haematology. But your articles and remarks on how to improve are very welcome too.

I wish you enjoyable reading,

Jan Van Droogenbroeck , MD, PhD, haematologist
Editor-in-chief

Musculoskeletal manifestations in children with acute lymphoblastic leukaemia

H. Mulder, N. Herregods, V. Mondelaers, Y. Benoit, B. De Moerloose

Acute lymphoblastic leukaemia (ALL) is the most common kind of childhood malignancy. Although the vast majority of patients are presented with medullary signs and symptoms such as an abnormal blood count, about one third will initially be presented with musculoskeletal complaints (with or without radiological abnormalities) as the only apparent abnormality. These skeletal manifestations in ALL are not pathognomonic and may mimic several orthopaedic conditions, such as juvenile rheumatoid arthritis, osteomyelitis, septic arthritis and transient synovitis. This may therefore contribute to a delay in diagnosis, resulting in higher morbidity and mortality rates. However, musculoskeletal manifestations in leukaemia are usually associated with a precursor-B-ALL and have a good prognosis.

The purpose of this review is to highlight the diagnostic pitfalls in this type of ALL. ALL should always be considered as a differential diagnosis in any child with unexplained or persistent bone pain and a bone marrow examination is highly recommended when steroid therapy is being considered.

(Belg J Hematol 2012;3:3-11)

Introduction

Leukaemia is the most common childhood malignancy accounting for 30-40% of all malignancies. Acute lymphoblastic leukaemia (ALL) is the most common subtype with a frequency up to 85% and a peak incidence at age 2-6 years.[1] Leukaemias are heterogeneous in clinical presentation and course. Due to excessive clonal proliferation of leukaemic blasts and their impaired differentiation, normal haematopoiesis is disrupted and results in bone marrow failure. Hence, patients characteristically are presented with signs and symptoms such as pallor, fever, anorexia, lethargy, lymphadenopathy, organomegaly and variable haematological abnormalities (anaemia, thrombocytopenia, leukopaenia/leukocytosis and circulating blasts). Moreover, a third of paediatric patients with ALL initially are presented with complaints associated with the musculoskeletal system.[2,3] Sometimes these manifestations are the only symptoms at presentation and therefore may mask ALL when peripheral blood changes are subtle or even absent. In the literature, several reports can be found in which musculoskeletal manifestations (MSM) and near normal haematological variables are associated with immunophenotypes consistent with precursor-B-ALL.[2,4-11]

Localised or diffuse bone pain, limping, arthritis, myalgia and failing to use an extremity are the most

Authors: H. Mulder[1], N. Herregods[2], V. Mondelaers1, Y. Benoit[1] and B. De Moerloose.[1] [1]Department of Paediatric Haematology-Oncology and Stem Cell Transplantation, Ghent University Hospital, Ghent, [2]Department of Radiology, Ghent University Hospital, Ghent

Please send all correspondence to: B. De Moerloose, Department of Paediatric Haematology-Oncology and Stem Cell Transplantation, Ghent University Hospital, 3K12D, De Pintelaan 185, 9000 Ghent, Belgium; tel: 0032 933 26417, email: barbara.demoerloose@uzgent.be.

Conflict of interest: The authors have nothing to disclose and indicate no potential conflicts of interest.

Key words: acute lymphoblastic leukaemia, musculoskeletal manifestation, bone pain.

Pseudohyperkalaemia in T-ALL: how to avoid life-threatening hypo-kalaemia

N. Reynaert, V. Labarque, A. Uyttebroeck, E. Levtchenko, M. Renard

Tumour lysis syndrome is a well-known life-threatening complication in children with acute leukaemia and hyperleukocytosis. It is characterised by hyperkalaemia but it should be distinguished from pseudohyperkalaemia. Various underlying factors for this phenomenon of pseudohyperkalaemia have been suggested. Here, we describe two children with T-cell acute lymphoblastic leukaemia who presented with hyperleukocytosis and hyperkalaemia, in whom the diagnosis of pseudohyperkalaemia was made. We demonstrate that in extreme leukocytosis the use of a vacuum system, pneumatic transport, and sample centrifugation contribute all together to pseudohyperkalaemia. As the leukocyte count decreases, plasma potassium levels are more reliable. Based on our results we suggest to measure potassium in a whole blood sample immediately brought to the laboratory for minimising false results due to ex vivo cell lysis.

(Belg J Hematol 2012;3:12-6)

Introduction

Acute leukaemia is the most common cancer in childhood and represents one third of all cancers in children younger than 16 years. Acute lymphoblastic leukaemia (ALL) represents 75-80% of all acute leukaemia in children. T-cell ALL, in particular, is characterised by high leukocytosis (>50x10^9/l white blood cells (WBC)) and a high number of blasts in the peripheral blood and bone marrow at diagnosis.[1]

Tumour lysis syndrome is a well-known severe complication caused by rapid and massive breakdown of tumour cells. It occurs most frequently in patients with rapidly proliferating haematologic malignancies, such as ALL with high tumour load (>100x10^9/l WBC). Usually, this complication is seen after the initiation of cytotoxic therapy, but spontaneous tumour lysis may occur. The massive release of intracellular contents overwhelms the normal homeostatic mechanism and causes hyperuricaemia, hyperkalaemia, hyperphosphataemia and hypocalcaemia. These metabolic abnormalities, but mainly hyperkalaemia, can lead to morbidity and mortality due to cardiac arrhythmias, kidney failure and convulsions. Hence, a rapid and adequate treatment of this complication is required.[2] In patients with extreme hyperleukocytosis, pseudohyperkalaemia is also described. It is defined by a false elevation in serum or plasma potassium levels not reflecting in vivo potassium values.[3,4,5,6] Yet, early detection of this phenomenon is mandatory to prevent unnecessary intensive therapy and serious consequences of iatrogenic hypokalaemia.

In this article we describe two patients with T-cell

Authors: N. Reynaert, MD[1], V. Labarque, MD, PhD[1], A. Uyttebroek, MD, PhD[1], E. Levtchenko, MD, PhD[2], M. Renard , MD[1], [1]Department of Pediatric Haemato-Oncology, University Hospitals Leuven, Belgium. [2]Department of Pediatric Nephrology, University Hospitals Leuven, Belgium.

Please send all correspondence to: N. Reynaert, University Hospitals Leuven, Herestraat 49, 3000 Leuven, e-mail: nele.reynaert@uzleuven.be.

Conflict of interest: The authors have nothing to disclose and indicate no potential conflict of interest.

Key words: Pseudohyperkalaemia, hyperleukocytosis, pneumatic transport, whole blood potassium, children

Clofarabine in clinical haematology

T. Lodewyck

Clofarabine is a second-generation nucleoside analogue which has been rationally developed with the aim to combine the therapeutic qualities and avoid the toxic limitations of fludarabine and cladribine. Clofarabine has been reimbursed in Belgium for the treatment of paediatric patients up to the age of 21 years with relapsed or refractory Acute Lymphatic Leukaemia (ALL) after two or three preceding regimens respectively. Clinical efficacy has also been demonstrated in newly diagnosed and advanced Acute Myoblastic Leukaemia (AML). The drug is currently being investigated in several randomised trials in AML and ALL and as part of the conditioning regimen prior to stem cell transplantation. This article focuses on the pharmacology, toxicity and clinical efficacy of clofarabine.
(Belg J Hematol 2012;3:17-22)

Introduction

Clofarabine is a second-generation nucleoside analogue and is structurally related to fludarabine and cladribine which are widely used in the treatment of lymphoproliferative disorders.[1] The drug has been rationally designed in an attempt to combine the therapeutic qualities and overcome the toxic limitations of its congeners. Although developed in the 1980's, there has been little interest in its development until 1993 when the first preclinical and animal studies were initiated at MD Anderson Cancer Center. Human phase I trials took off in 1998 and the drug was approved by the Food and Drug Administration (FDA) in 2004 for treatment of relapsed and refractory ALL in children and adolescents up to the age of 21 years. Approval by the European Medicines Agency (EMA) followed in 2006. Clofarabine has been reimbursed in Belgium for patients ≤21 years with relapsed or refractory ALL having received two or three preceding regimens respectively. This article reviews the pharmacology, toxicities and clinical efficacy of clofarabine.

Pharmacology: molecular structure and mechanism of action

Two features characterise the molecular structure of clofarabine [2-chloro-9-(2'-deoxy-2'-fluoro-b-d-arabinofuranosyl)-9H-purine-6-amine; Cl-F-ara-A; CAFdA; 2-chloro-9-(2'-deoxy-2'-fluoro-beta-D-arabinofuranosyl)-adenine].[1] As illustrated in *Figure 1*, clofarabine has a chloro-atom at the 2-position of the adenine ring which confers resistance to degradation by intracellular adenosine deaminase. Halogenation at the 2-position of adenine is also the case for fludarabine (fluor-atom) and cladribine (chloro-atom) which are equally resistant to deamination. However, in contrast to its congeners, clofarabine has an additional fluorine at the 2'-position of the ribose ring. This modification renders the drug less susceptible to bacterial E. coli purine nucleoside phosphorylase in the gastrointestinal (GI) tract and increases its resistance to hydrolysis in acidic environments. Purine nucleoside phosphorylase may cleave the glycosidic bond between the ribose and purine ring of fludarabine and cladribine. This may lead to the production of a halogenated adenine which is a neurotoxic

Author: T. Lodewyck, MD, Department of Hematology, AZ Sint-Jan Brugge-Oostende AV, Ruddershove 10, 8000 Brugge, e-mail: tom.lodewyck@azsintjan.be.

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Key words: Clofarabine, acute leukaemia, nucleoside analogue.

Current Clinical Trials

(Belg J Hematol 2012;3:23)

B-Will study: National Survey of Von Willebrand Disease in Belgium

Von Willebrand Disease – survey – typing

Von Willebrand's disease (VWD) is an autosomally inherited bleeding disorder caused by a deficiency or abnormality of Von Willebrand factor (VWF). VWF is a multimeric adhesive protein playing an important role in primary haemostasis by promoting platelet adhesion to the subendothelium at sites of vascular injury and platelet-platelet interactions in high shear-rate conditions. It is also the carrier of factor VIII (FVIII), thus indirectly contributing to the coagulation process. VWD has a prevalence of approximately 1% in the general population, but the figure for clinically relevant cases is lower (about 100/million inhabitants). Bleeding manifestations are heterogeneous: mucosal bleeding is typical of all VWD cases but haemarthrosis and haematomas may also be present when FVIII levels are low. Most cases appear to have a partial quantitative deficiency of VWF (type 1 VWD) with variable bleeding tendency, whereas qualitative variants (type 2 VWD), due to disfunctional VWF, are clinically more homogeneous. Type 3 VWD is rare, and the patients have a moderate to severe bleeding diathesis because of the virtual absence of VWF, and a recessive pattern of inheritance. No data are available on the number of VWF patients in Belgium. VWD is frequently not diagnosed in milder forms of the disease and often incomplete in other forms.

The B-Will study is a national survey of patients diagnosed with Von Willebrand's disease in Belgium through university hospitals and larger regional hospitals: frequency, type, distribution, bleeding phenotype, underlying mutation.

Patients will be asked to agree to an interview in which their bleeding phenotype will be established through the filling in of the ISTH Bleeding Score, and blood sampling will be done for analysis. Full laboratory characterisation and (sub)typing of VWD patients will be done at the Antwerp University Hospital with all available techniques, including identification of causative molecular abnormalities in the VWF gene. Furthermore, frozen plasma and DNA samples will be kept for further future research into VWD (VWD-Biobank).

Patients suspected of having VWD can be included:

Type 3: VWF:Ag and VWF:RCo <5%

Type 2: Decreased Ristocetin Induced Platelet Aggregometry RIPA (concentration 1.2-1.5 mg/dl) and/or VWF:RCo/VWF:Ag < 0.7 (type 2A/2M)
or
unexplained thrombocytopenia where there is a suspicion of VWD and/or positive low concentration RIPA (0.8mg/ml) (type 2B)
or
all patients with VWF:CB/VWF:AG ratio < 0.7 (type 2A, Collagen type)
or
FVIII:c/VWF:Ag <0.5 (type 2N)

Type 1: VWF:Ag< 35%

This study has been initiated by the Hemostasis Unit of the Antwerp University Hospital (UZA) (prof dr Alain Gadisseur) and has the support of the Belgian Society on Thrombosis & Hemostasis (BSTH). The protocol received Ethical Committee approval in several university and affiliated hospitals at the end of 2011. Interested parties can contact the principal investigator for more information.

For more information, please contact:
Study coordinator: Prof dr Alain Gadisseur, MD PhD,
Department of Hematology,
CSL Behring Chair in Von Willebrand Disease
(Antwerp University), Antwerp University Hospital,
(UZA), Wilrijkstraat 10, 2650 Edegem.
T: 03 821 3779, F: 03 821 4286
e-mail alain.gadisseur@uza.be

Development of a clinical leukaemia vaccine using dendritic cells loaded with the Wilms' tumour (WT1) gene product

A. Van Driessche, V.F.I. Van Tendeloo, Z.N. Berneman

Dendritic cell (DC)-based vaccination holds promise as an adjuvant immunotherapy for many cancers. The Wilms' tumour (WT1) protein is overexpressed in most types of leukaemia and in many solid tumours. Therefore, WT1 could be regarded as a broadly applicable tumour-associated antigen in DC-based immunotherapy. In this thesis, we pursued the aim to enhance antileukemic immune response by the activation of WT1-specific T cells. We developed - from bench to bedside - a therapeutic vaccine of DC loaded with WT1 for patients with acute myeloid leukaemia (AML).

(Belg J Hematol 2012;3:24-6)

Introduction

During the last two decades, tremendous efforts have been made to improve treatment of cancer. Despite major advances in standard treatment, many patients relapse or progress after a period of time. Cancer immunotherapy is being extensively investigated as a treatment with less side-effects impacting on quality of life as compared to classical therapies. Dendritic cells (DC) are professional antigen-capturing and antigen-presenting cells and play a pivotal role in the activation of innate and adaptive immunity, as well as in the maintenance of peripheral tolerance.[1] In 2001, we have reported on a novel and effective approach to load in vitro generated human DC with tumour-associated antigens. A cytoplasmic non-viral gene delivery system was developed, based on transfection of in vitro transcribed mRNA encoding the full-length antigen into DC by electroporation.[2] This represents a very attractive procedure as mRNA-loaded DC have been shown to stimulate antigen-specific T cells in vitro and in vivo.[3] Furthermore, it is a method of gene transfer that is clinically safe, as mRNA has a relatively short half-life, results in transient protein expression and lacks the potential to integrate into the host genome.[4]

Wilms' tumour protein 1 (WT1) was chosen as a target antigen. This antigen has been described by several authors as an immunogenic protein which

Authors: ms. A. Van Driessche, MSc PhD, Quality Manager of Cell and Tissue Bank, Antwerp University Hospital, Antwerp, Belgium; V.F.I. Van Tendeloo, MSc PhD, Professor at Faculty of Medicine, University of Antwerp and Scientific Director, Center for Cell Therapy and Regenerative Medicine, Antwerp University Hospital, Antwerp, Belgium; Z.N. Berneman, MD PhD, Professor of Hematology, University of Antwerp and Head of division of Hematology, Antwerp University Hospital, Antwerp, Belgium. All authors: Laboratory of Experimental Hematology, Vaccine & Infectious Disease Institute (VaxInfection), Faculty of Medicine and Health Sciences, University of Antwerp, Antwerp, Belgium & Center for Cell Therapy and Regenerative Medicine (CCRG), Antwerp University Hospital (UZA), Edegem, Belgium.

Please send all correspondence to: ms. A. Van Driessche, MSc PhD, Quality Manager Cell and Tissue Bank, Center for Cell Therapy and Regenerative Medicine (CCRG). Antwerp University Hospital (UZA), Wilrijkstraat 10. B-2650 Edegem, Belgium, e-mail: ann.van.driessche@uza.be.

Conflict of interest: The authors have nothing to disclose and indicate no potential conflicts of interest.

Key words: Acute myeloid leukaemia, immunotherapy, dendritic cells, Wilms' tumour protein 1, WT1.

Best of ASH

Highlights of the 53rd Annual Meeting of the American Society of Hematology (ASH)
December 10-13, 2011, San Diego, USA

A. Bosly

In the plenary session of the 53rd Annual Meeting of the American Society of Hematology (ASH) December 10-13, 2011, San Diego, USA, six oral presentations were selected as the most important contributions to progress in haematology in 2011.
(Belg J Hematol 2012;3:27-8)

1: Gene transfer in haemophilia B

The hottest topic is clearly the Nathwani abstract on gene transfer in haemophilia B. This phase I study performed in the United Kingdom (UK) utilises an adenoassociated virus (AAV8) capsid as vector for Factor IX without immunosuppression to treat six patients with severe haemophilia B. All patients responded (four have discontinued prophylaxis and were free of spontaneous haemorrhage and two increased the interval between FIX prophylaxes).
Administration by IV of vector and coagulation factor IX codon was well-tolerated and durable maintenance of 2-11% of FIX was observed. One patient has an increase of transaminases related to specific T cells against AAV8 capside. Short course of prednisone normalised enzymes.

2. PB and BM compared

Recombinant G-CSF mobilised peripheral blood (PB) is largely used instead of bone marrow (BM) as source of stem cells for transplantation because of more rapid reconstitution of haematopoiesis and more convenient for donor. Anasetti from the United States (USA) reported a prospective randomised trial comparing PB to BM as source of stem cells for allogeneic transplantation from unrelated donors in 550 patients. Overall survival was not different (51 % for PBSC, 48 % for BM, $p = 0.288$). Disease-free survival (DFS), relapse, non-relapse mortality, acute Graft Versus Host Disease (GVHD), number of hospitalisation day during the first year were not significally different. Chronic GVHD was superior for PBSC ($p = 0.014$) and graft failure was superior in BM ($p = 0.002$). By contrast, in another study in sibling donors, no decrease in relapse in case of PBSC was observed, maybe due to the low number of CML patients in this study, a situation where the effect of GVH to decrease relapse is more evident. The conclusion of the authors is that in a standard case, both sources could be used in accordance to patient/donor preference. PBSC is preferred in case of risk for graft failure and high risk for severe infection due to 5 and 7 days faster for neutrophil and platelets recovery.

3. Megakaryocyte cell line

Takayama et al. from Japan were able to immortalise in mice a megakaryocyte cell line (MKCL) depending to activation by cMYC and BMI 1. This cell line can produce platelet in vitro and these platelets exhibit normal functions in vivo. Potential utilization in humans of these mice experiences could probably be restricted by economical problems.

Author: André Bosly, MD PhD, Haematology, CHU Mont-Godinne, UCL and Narilis.

Conflict of interest: the author has nothing to disclose and indicates no potential conflicts of interest.

International & national congresses	
April 1-4, 2012	**38th Annual Meeting of the European Group for Blood and Marrow Transplantation (EBMT),** Geneva, Switzerland For more information please visit: www.congrex.ch/ebmt2012
April 12-13, 2012	**13th Annual Network for Advancement of Transfusion Alternatives (NATA) Symposium,** Copenhagen, Denmark For more information please visit: www.nataonline.com
April 18-20, 2012	**The International Haemapheresis Congress (European Society for Haemapheresis (ESFH) Joint Congress),** The Hague, The Netherlands For more information please visit: www.hemaferesecongres.nl
April 20-22, 2012	**European School of Haematology (ESH): ESH-EHA Scientific Workshop on Mesenchymal Stem Cells,** Mandelieu, France For more information please visit: www.esh.org/conferences/
April 22-25, 2012	**European School of Haematology (ESH): ESH-EBMT Training Course on Haemopoietic Stem Cell Transplantation,** Sofia, Bulgaria For more information please visit: www.esh.org/conferences/
April 25-27, 2012	**14th Annual International Haemovigilance Network (IHN) Symposuim,** Montreal, Canada For more information please visit: www.ihn-org.com
April 25-27, 2012	**24th Internistendagen,** Maastricht, The Netherlands For more information please visit: www.internistendagen.nl
April 25-28, 2012	**34th World Congress of the International Society of Hematology (ISH),** Cancun, Mexico For more information please visit: www.ishworld.org
April 26-28, 2012	**Great Debates and Updates in Hematologic Malignancies,** New York, United States For more information please visit: www.imedex.com
May 3-5, 2012	**The Thrombosis and Hemostasis Summit of North America (THSNA),** Chicago, United States. For more information please visit: www.thsna.org
May 9-12, 2012	**25th Annual Meeting American Society of Pediatric Hematology Oncology (ASPHO),**New Orleans, United States For more information please visit: www.aspho.org
May 10-13, 2012	**12th European Symposium on Platelet and Granulocyte Immunobiology,** Warsaw, Poland For more information please visit: www.espgi2012.pl
May 21-24, 2012	**25th International Symposium on Technological Innovations in Laboratory Hematology (ISLH),** Nice, France For more information please visit: www.islh.org

Calendar of events

International & national congresses	
May 23-24, 2012	**IPFA/PEI 19th International Workshop on "Surveillance and Screening of Blood Borne Pathogens",** Budapest, Hungary For more information please visit: www.ipfa.nl/events
May 23-24, 2012	**Nederlandse Vereniging voor Bloedtransfusie (NVB) Symposium Transfusiegeneeskunde 2012,** Ede, The Netherlands For more information please visit: www.nvbtransfusie.nl
May 24-27, 2012	**European School of Haematology (ESH): ESH International Conference on Myelodysplastic Syndromes**, Dublin, Ireland For more information please visit: www.esh.org/conferences/
June 1-5, 2012	**American Society of Clinical Oncology (ASCO) 2012 Annual Meeting,** Chicago, United States For more information please visit: www.asco.org
June 14-17, 2012	**17th Congress of European Hematology Association (EHA),** Amsterdam, The Netherlands. For more information please visit: http://www.ehaweb.org
June 27-30, 2012	**58th Annual SSC Meeting (Scientific & Standardisation Committee of the ISTH),** Liverpool, United Kingdom For more information please visit: www.isth.org
July 7-12, 2012	**32nd International Congress of the International Society of Blood Transfusion (ISBT),** Cancun, Mexico For more information please visit: www.isbtweb.org
August 17-19, 2012	**5th Mayo Clinic Angiogenesis Symposium,** Minneapolis, United States For more information please visit: www.mayo.edu/cme/hematolgy-and-oncology
August 18-22, 2012	**The 30th World Congress of Biomedical Laboratory Science,** Berlin, Germany For more information please visit: www.paragon-conventions.com
August 23-26, 2012	**41st Society for Hematology and Steam Cells (ISEH) Annual Scientific Meeting,** Amsterdam, The Netherlands For more information please visit: www.iseh.org
September 5-7, 2012	**The Annual General Meeting of International Society of Pediatric Oncology: European Neuroblastoma Group (SIOPEN),** Gent, Belgium For more information please visit: https://www.siopen-r-net.org/
September 20-23, 2012	**European School of Haematology (ESH): ESH-iCMLf International Conference: Biology and Therapy,** Baltimore, United States For more information please visit: www.esh.org/conferences/
October 4-6, 2012	**European School of Haematology (ESH): ESH International Conference on Myeloproliferative Neoplasms,** Vienna, Austria For more information please visit: www.esh.org/conferences/