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# 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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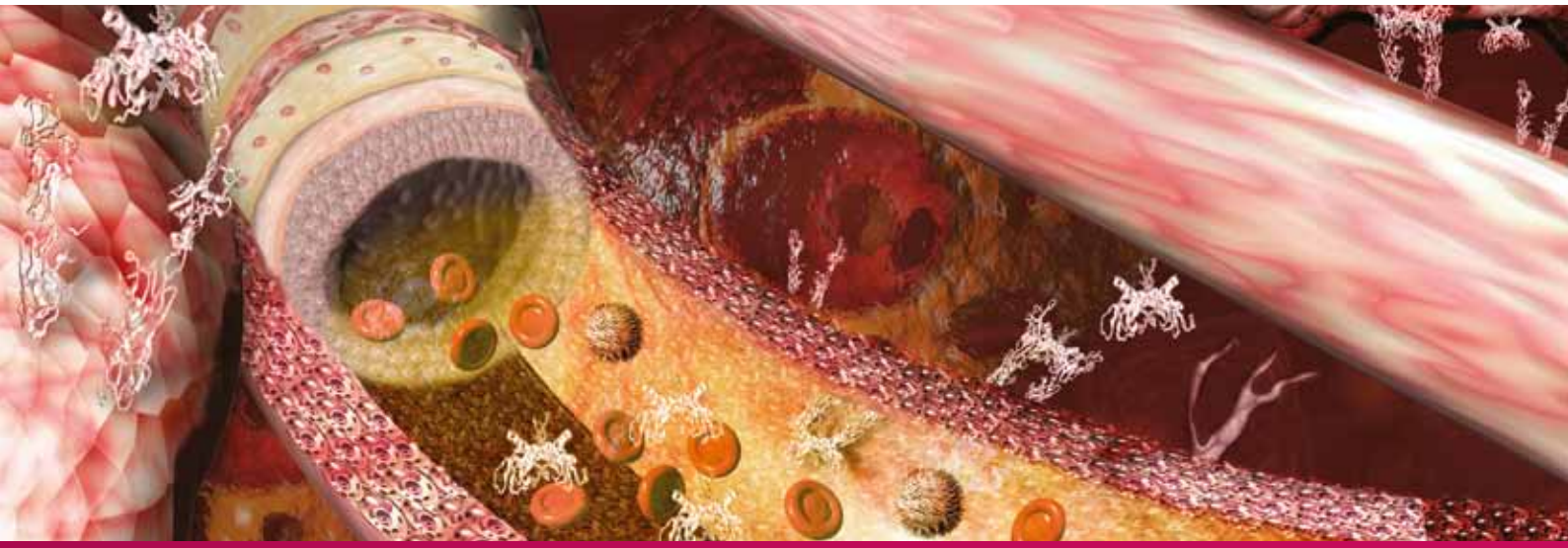



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De BJH aims to be a peer-reviewedhematology journal covering all aspects of the diagnostic and clinical management of hematology patients, reflecting a multidisciplinary approach to therapy. It aims informing clinicians active in the field of hematology 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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Volume 4, Issue 4, December 2013

# Introduction

Dear Reader,

Another year has disappeared into the haze of eternity and I do hope you enjoyed 2013 on a personal and professional level. I would like to begin by wishing you and your loved ones all the best for a healthy and successful 2014!

Several of us attended/will attend the ASH and/or upcoming BHS annual meetings, but I'm convinced there'll be something of interest for everyone in this issue of the BJH too.

Light chain amyloidosis is very probably underdiagnosed, and when diagnosed, often in a late stage, though new molecules have recently changed the treatment and outcome of this disorder. The first article in this issue of the BJH provides a clear overview.

Myelofibrosis is another often-frustrating disease, where the therapeutic options are changing very rapidly. The contribution to this issue on myelofibrosis covers clinical guidelines.

With articles covering asparaginase and childhood ALL, an intriguing case report and an instructive summary of a trial on haploidentical stem cell transplantation, there will be something to everyone's taste and interest.

I wish you enjoyable reading,

Dr Jan Van Droogenbroeck
*Editor in chief*

# Light chain amyloidosis in the era of novel agents

K. Beel, MD, PhD[1]

**The development of new immunomodulatory therapies and their implementation in the treatment of multiple myeloma in the past years, offer new perspectives for the treatment of other plasma cell dyscrasias. Light chain amyloidosis is historically associated with a very poor prognosis, despite the small size of the monoclonal plasma cell population, due to progressive amyloid deposition in vital organs. Hence, advances in treatment are eagerly awaited. Luckily, myeloma patients are paving the way for light chain amyloidosis treatment, clearly demonstrating that immunomodulatory drugs and proteasome inhibitors are capable of controlling plasma cell proliferation. Two recently published trials have shown a remarkable survival benefit with CyBorD, a bortezomib containing regimen in light chain amyloidosis, possibly setting a new standard for the treatment of this disease. In this article, we review current insights in the pathogenesis, diagnostic challenges, prognostic markers and available treatments for light chain amyloidosis.**
*(Belg J Hematol 2013;4(4):120-126)*

## Introduction

Systemic light chain amyloidosis (AL) is caused by a small clone of plasma cells, synthesising immunoglobulin light chain polypeptides, which are prone to misfolding and interstitial deposition as insoluble β-sheet fibrils. Without treatment, the associated proteotoxicity inevitably leads to progressive organ failure and death. AL occurs in approximately one case per 100 000 persons in western countries, similar to chronic myeloid leukaemia, with a mean age of 63 years at diagnosis. Historically, AL had a very poor prognosis, with a median survival of thirteen months.[1] Although AL is the most common type of systemic amyloidosis; hereditary, senile and secondary forms exist and should not be confused with AL because of the different therapies indicated. An overlap with multiple myeloma (MM) exists, as 20% of AL patients meet the criteria for myeloma and up to 30% of myeloma patients have minor amyloid deposition.[2] As opposed to other plasma cell disorders, a 1:3 κ:λ ratio is found in AL, which supports the concept that λ light chains are intrinsically more amyloi-dogenic than κ.[3] Some cytogenetic abnormalities occur both in MM and in AL. The translocation t(11;14) is more frequent in AL (40-50%), but in contrast to MM, it is associated with a worse prognosis, as is the presence of cyclin D1 overexpression. Of interest, marrow plasma cells of amyloidosis patients exert an intermediate gene expression profile between a normal and a myeloma signature.[4]

## Pathogenesis

The process of amyloid formation is not completely understood. Like Parkinson's disease and Alzheimer's, AL is a proteopathy, meaning that changes in protein conformation induce toxicity through highly ordered amyloid β-sheet depositions. AL amyloidosis is inherently linked to the adoptive immune response in jawed vertebrates. Immunoglobulin formation in the plasma cell relies on recombination and somatic gene mutations. However, genetic plasticity has its downside and amyloid formation could be considered the price for the acquisition of a sophisticated adoptive immune system. It is assumed that the amyloid deposition process was

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**Conflict of interest:** The author has nothing to disclose and indicates no potential conflict of interest.

**Key words:** diagnosis and treatment of AL amyloidosis, novel agents in AL amyloidosis, systemic immunoglobulin light chain amyloidosis.

# Disease characteristics in Belgian myelofibrosis patients and management guidelines anno 2013

T. Devos, MD, PhD[1], N. Straetmans, MD, PhD[2], C. Schuermans, MD[3], S. Benghiat, MD, PhD[4], V. Robin, MD[5], P. Lewalle, MD, PhD[6], P. Mineur, MD[7], G. Verhoef, MD, PhD[1], L. Knoops, MD, PhD[8]

**Diagnostic and management guidelines for myelofibrosis patients are presented in this paper. As a consequence of the rapid evolution and progress in this domain over the last years, the need was felt by the BHS MPN subcommittee to update these guidelines for our country. The different prognostic scores in myelofibrosis, the diagnostic tools and treatment options with the focus on new possibilities are discussed.**
*(Belg J Hematol 2013;4(4):127-137)*

## Introduction

Myelofibrosis (MF) is the Philadelphia-chromosome negative myeloproliferative neoplasm (MPN) with the lowest incidence but the worst prognosis. MF can be primary (PMF) or can develop from an earlier existing PV (PPV-MF) or ET (PET-MF). MF is a progressive, chronic myeloid neoplasm resulting in intramedullary fibrosis, progressive cytopenia, splenomegaly and debilitating constitutional symptoms. The estimated incidence of PMF is 0.5 - 1.5 per 100 000 with a median age of 67 years.[1]

The diagnosis of PMF is based on the 2008 World Health Organization (WHO) criteria.[2] The diagnosis of PPV-MF and PET-MF should be made according to IWG-MRT criteria.[3] Leukemic transformation should be called blast-phase MF.[4] These criteria are described in *Table 1*. The identification of prefibrotic PMF is still a matter of debate and will not be discussed in this paper. Over the last years, different prognostic markers have been identified, leading to three consecutive prognostic scores in three years time: the International Prognostic Scoring System (IPSS), the Dynamic International Prognostic Scoring System (DIPSS) and the DIPSS plus.[5-7] These scores have been of high value for the development of a novel risk-adjusted therapy in MF.

The description of the JAK2 V617F mutation in 2005, present in about 60% of MF patients, profoundly changed the diagnostic and therapeutic landscape of MF. It revealed the crucial role played by the JAK/STAT pathway in the pathogenesis of MPN and opened the way for the development of small ATP-competitive molecules, the JAK tyrosine kinase inhibitors.

Moreover, other progresses were accomplished in recent years: improvement of reduced intensity conditioning (RIC) regimens for allogeneic hematopoietic stem cell transplantation, better supportive care measures and the development of new molecules explored in different clinical trials.

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**Conflict of interest:** The scientific survey on MF disease characteristics in Belgium has been financed by Novartis.

**Key words:** guidelines, JAK2 inhibitors, myelofibrosis, prognostic scores.

# PEG-asparaginase in the treatment of childhood acute lymphoblastic leukaemia

V. Mondelaers, MD[1], T. Bauters, PharmD, PhD[2], B. De Moerloose, MD, PhD[1], Y. Benoit, MD, PhD[1]

**Asparaginase is an essential compound of combination chemotherapy in acute lymphoblastic leukaemia in children and adults. Essentially, three preparations of asparaginase are used in childhood acute lymphoblastic leukaemia: native Escherichia coli asparaginase, Erwinia chrysanthemi asparaginase and PEG-asparaginase. Although PEG-asparaginase seems to have some advantages over the other asparaginase preparations, its clinical use in Europe is limited to second-line therapy after allergic reactions to native asparaginase. This is in contrast to the United States, where PEG-asparaginase has been approved as first-line treatment of children with acute lymphoblastic leukaemia. This report describes the properties, clinical benefits and side effects of PEG-asparaginase.**

*(Belg J Hematol 2013;4(4):138-143)*

## Introduction

Asparaginase is a potent antitumor agent used in the treatment of childhood acute lymphoblastic leukaemia (ALL) for over 40 years. Asparaginase, a high molecular weight enzyme, depletes plasma asparagine by hydrolysing asparagine in aspartic acid and ammonia. Exposure of lymphoblasts to asparaginase results in inhibition of protein synthesis and subsequent cell death by the incapacity to produce intracellular asparagine.[1]

Combination chemotherapy to induce remission in childhood ALL patients usually consists of asparaginase together with corticosteroids, vincristine and anthracyclines, resulting in remission induction rates of 90 to 100%.[2,3] The main drawbacks for the use of asparaginase are the adverse effects on normal protein synthesis and the frequent hypersensitivity reactions.

Currently, three preparations of asparaginase are used to treat frontline and relapsed ALL in children: native Escherichia coli (E. coli) asparaginase, Erwinia chrysanthemi asparaginase and PEG-asparaginase, a form of native E. coli asparaginase linked to a polyethylene glycol monomethyl ether. These preparations differ in activity, pharmacokinetics and immunising capacity. The approval for first- or second-line treatment differs in the United States and Europe.[4] This review focuses on the use of PEG-asparaginase (Oncaspar®) in childhood ALL.

## Chemistry

PEG-asparaginase (polyethylene glycol-L-asparaginase, Oncaspar®, Medac, Germany), a modified version of E. coli asparaginase, is produced by covalent conjugation of monomethoxy polyethylene glycol (PEG) to E. coli asparaginase, more specifically to enzyme sites that are not active. Pegylation blocks potentially immunogenic epitopes and reduces the dose limiting hypersensitivity reactions that are associated with native E. coli asparaginase. In addition, it delays the elimination of the enzyme by prolonging the half-life of the drug (5.5 versus 1.2 days).[5] The prolonged half-life of PEG-asparaginase allows for dosing once every fourteen days, which obviates the need for long hospitalisations or multiple visits to day-clinics.

In patients who were previously treated with E. coli asparaginase with documented hypersensitivity reactions, pharmacokinetics of PEG-asparaginase can be adversely

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

**Key words:** acute lymphoblastic leukaemia, efficacy, paediatrics, PEG-asparaginase, side effects.

# Cost-minimisation analysis of PEG-L-Asparaginase versus native L-Asparaginase for the treatment of children with acute lymphoblastic leukaemia in Belgium

T. Bauters, PharmD, PhD[1], V. Mondelaers, MD[2], B. De Moerloose, MD, PhD[2], H. Robays, PharmD[1], Y. Benoit, MD, PhD[2]

**PEG-L-Asparaginase (Oncaspar®) is a major compound of antineoplastic combination therapy for reinduction in acute lymphoblastic leukaemia in children and adults with known hypersensitivity. In the United States, it has been approved for many years as first-line treatment of children with acute lymphoblastic leukaemia. Its clinical benefits have been extensively described. In this report, a cost-minimisation analysis comparing the direct cost of PEG-L-asparaginase with that of native E. coli and Erwinia L-asparaginase treatment is described.**

*(Belg J Hematol 2013;4(4):144-147)*

## Introduction

Acute lymphoblastic leukaemia (ALL) is the most common childhood cancer, accounting for approximately one quarter of new cancer diagnoses in children. The combination of Escherichia coli L-asparaginase, vincristine and prednisone treatment has increased the remission induction rate to more than 95% in patients with standard risk ALL. L-asparaginase (further referred to as Asparaginase) has been shown to be a crucial chemotherapeutic agent in ALL treatment.[1-4]

Asparaginase is an enzyme that catalyses the hydrolysis of extracellular asparagine to ammonia and aspartic acid in the bloodstream and the extracellular space. Normal cells are capable of synthesising asparagine, which is essential for cell survival. Certain malignant cells, especially leukemic lymphoblasts, however are not and depend on extracellular sources of asparagines for protein synthesis.[5]

The sources of asparaginase for hospital use are bacterial in origin, mainly Escherichia coli (E. coli) and Erwinia chrysanthemi. Native asparaginase is commercially available in two forms: E. coli (Paronal®, Nycomed) and Erwinia (Erwinase®, Eusapharma, Jazz Pharmaceuticals). The frequency of hypersensitivity reactions to E. coli is rather variable (~40%) but ranges from 0 to 75% depending on the publication.[6,7] In case of hypersensitivity reactions (i.e. generalised reaction including pain, erythema, pruritus, angioedema, fever, respiratory distress or a localised reaction or a combination of both), discontinuation of E. coli asparaginase and substitution with Erwinia- or polyethylene glycol (PEG)-asparaginase (Oncaspar®, Sigma-Tau) is preferred.

In Belgium, E. coli asparaginase (Paronal®) is available and reimbursed in first-line treatment. Both Erwinia asparaginase (Erwinia®) and PEG-asparaginase (Oncaspar®) are not licensed in Belgium. They are reimbursed

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

**Key words:** acute lymphoblastic leukaemia, cost-minimisation analysis, paediatrics, PEG-L-Asparaginase.

# Haemolytic anaemia as an uncommon presentation of Hodgkin's lymphoma in a child

S. van Steijn, MD[1], A. Van Damme, MD, PhD[1], A. Malfroot, MD, PhD[1], J. van der Werff ten Bosch, MD, PhD[1]

**Haemolytic anaemia in childhood has an extensive differential diagnosis. We present a case of a twelve year old girl with haemolytic anaemia. A diagnosis of auto-immune haemolytic anaemia, probable Systemic Lupus Erythematosus was withheld. The girl was treated with immunosuppressive medication including prednisone and monoclonal anti-CD20 (Rituximab). After two years of follow-up a mediastinal mass was found and the diagnosis of Hodgkin's lymphoma was confirmed. She was treated with chemotherapy and radiotherapy with good response. This case reminds us that Hodgkin's lymphoma is not always an obvious diagnosis and that we should exclude this diagnosis in all patients with haemolytic anaemia or other auto-immune (like) manifestations.**

*(Belg J Hematol 2013;4(4):148-150)*

## Introduction

Haemolytic anaemia accounts for approximately 5% of all anaemia cases and some forms are more commonly diagnosed in African and Arabic populations. It is associated with significant morbidity and mortality and has an extensive differential diagnosis. Haemolytic anaemia can be due to non-immune mediated causes such as hereditary membrane defects (e.g. spherocytosis), haemoglobin defects (haemoglobinopathies) or enzyme defects (e.g. G6PD or pyruvate kinase deficiencies). Other acquired causes of non-immune haemolytic anaemia are liver disease, oxidant agents and micro-angiopathies. Immune-mediated causes of haemolytic anaemia are auto-immune haemolytic anaemia (AIHA) and Mycoplasma pneumonia or other infections (cold agglutinin disease).[1]

AIHA is rare in children. The incidence is estimated to be 1 in 80 000-100 000.[1] It is characterised by the presence of autoantibodies that bind to the erythrocyte surface membrane and lead to premature red cell destruction. When the haemolysis is initiated suddenly (acute haemolytic anaemia), the disease can be life threatening.

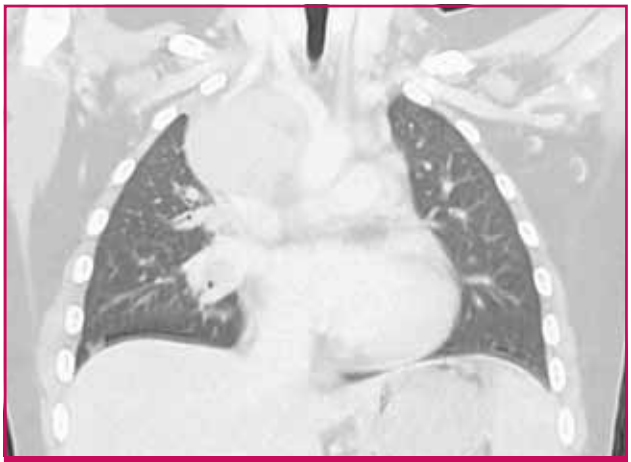

**Figure 1.** Chest CT scan revealing a mediastinal mass.

Chronic haemolytic anaemia on the other hand is characterised by less severe but nevertheless sometimes difficult to manage episodes of AIHA. AIHA can be based on the optimal temperature for antibody binding (warm versus cold antibodies) or based on the presence

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**Key words:** Auto-immune haemolytic anaemia, Hodgkin's lymphoma.

# A phase I/II single centre study of haploidentical transplantation combined with G-GSF, or GM-CSF, and escalating DLI in high-risk patients with no matched donors

P. Lewalle, MD, PhD[1], R. Rouas[1], D. Bron, MD, PhD[1], P. Martiat, MD, PhD[1]

**In 1999, we decided to start a phase I/II study of haploidentical transplantation for high-risk patients. The aim of the work was to implement a strategy to accelerate and strengthen the immune reconstitution by using nonspecific manipulation post-transplant and by developing specific strategies directed against viral antigens. The goal was to increase the graft-versus-leukemia effect without inducing or aggravating the deleterious graft-versus-host disease. The conditioning regimen, adapted to our group of patients, remained the same throughout. Importantly, the first recruited patients were in refractory disease, over time we were referred less advanced patients (complete remission 2 or more). There were 45 patients, all at high-risk, among which 27 were in refractory relapse. We questioned the importance of post-transplant growth factors policy and the influence of donor lymphocyte infusion. Because of the conditioning, transplant-related mortality was low at 3 months, but thereafter changed unfavourably when using granulocyte macrophage-colony stimulating factors in an increased incidence of acute graft-versus-host disease. As a whole the long-term survival of the patients was poor (18%) but improved a lot when transplanted patients were in complete remission (leukaemia-free survival of 39% at five years). Regarding the use of growth factors and donor lymphocyte infusion, granulocyte macrophage-colony stimulating factors with donor lymphocyte infusion induced a very high transplant-related mortality due to a high rate of severe graft-versus-host disease, while the combination of granulocyte colony-stimulating factors and a moderate dose of donor lymphocyte infusion was much safer but didn't overcome the high relapse rate in refractory patients. The combination of granulocyte colony-stimulating factors and donor lymphocyte infusion might nonetheless be sufficient to decrease the infection rate in patients transplanted in complete remission. The use of granulocyte macrophage-colony stimulating factors leads to an unacceptable lethal graft-versus-host disease rate. The 39% at five years leukaemia-free survival in patients in complete remission compares favourably with what can be achieved with matched unrelated donors in complete remission 2 or more.**
*(Belg J Hematol 2013;4(4):151-160)*

## Introduction

At the start of this study (in August 1999), we were confronted with, partly for ethnic reasons, and referred a non-negligible number of patients who had to be transplanted because of high-risk acute leukaemia or because they relapsed several times, and for which no matched donor was available. At this time, haploiden-

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

**Key words:** CMV, donor lymphocyte infusion, haploidentical transplantation, immunotherapy.

# Calendar of events

## International & national congresses 2014

| | |
|---|---|
| January 22-24 | **8th Dutch Hematology Congress**<br>Arnhem, The Netherlands<br>For more information please visit: http://www.hematologiecongres.nl/8th-dutch-hematology-congress/welkom.html |
| January 30-February 1 | **29th General Annual Meeting of the Belgian Hematological Society (BHS)**<br>Ghent, Belgium<br>For more information please visit: http://www.bhs.be/ |
| February 1 | **BVAC/ABCA Satellite Meeting during the general annual meeting of the BHS**<br>Ghent, Belgium<br>For more information please visit: www.cytometry.be |
| February 5-6 | **ESH Clinical Updates in Haematology on Lymphoid Neoplasms and Myeloma**<br>Paris, France<br>For more information please visit: http://www.esh.org/conferences/ |
| February 12-15 | **58th Annual Meeting Society of Thrombosis and Haemostasis Research (GTH)**<br>Vienna, Austria<br>For more information please visit: http://www.gth2014.org/ |
| February 14-15 | **5th International Hematologic Malignancies Conference: Bridging The Gap**<br>Taipei, Taiwan<br>For more information please visit: http://aphcon.org/btg2014.html |
| February 26-28 | **7th Annual Congress of the European Association for Haemophilia and Allied Disorders (EAHAD)**<br>Brussels, Belgium<br>For more information please visit: http://eahad2014.com/ |
| February 28-March 2 | **10th European Congress on Hematologic Malignancies: From Clinical Science to Clinical Practice**<br>Vienna, Austria<br>For more information please visit: http://www.imedex.com/hematologic-malignancies-european-congress/ |
| March 5-7 | **16th Annual International Haemovigilance Seminars (IHS) Symposium**<br>Barcelona, Spain<br>For more information please visit: http://www.ihn-org.com/ihn-symposium/ |
| March 30-April 2 | **40th European Group for Blood and Marrow Transplantation (EBMT) Annual Meeting**<br>Milan, Italy<br>For more information please visit: http://www.ebmt.org/Contents/Annual-Meeting/40thEBMTAnnualMeetingin2014/Pages/40th-EBMT-Annual-Meeting-in-2014.aspx |
| April 5-9 | **American Association for Cancer Research (AACR) Annual Meeting**<br>San Diego, USA<br>For more information please visit: http://www.aacr.org/home/scientists/meetings--workshops/aacr-annual-meeting-2014.aspx |