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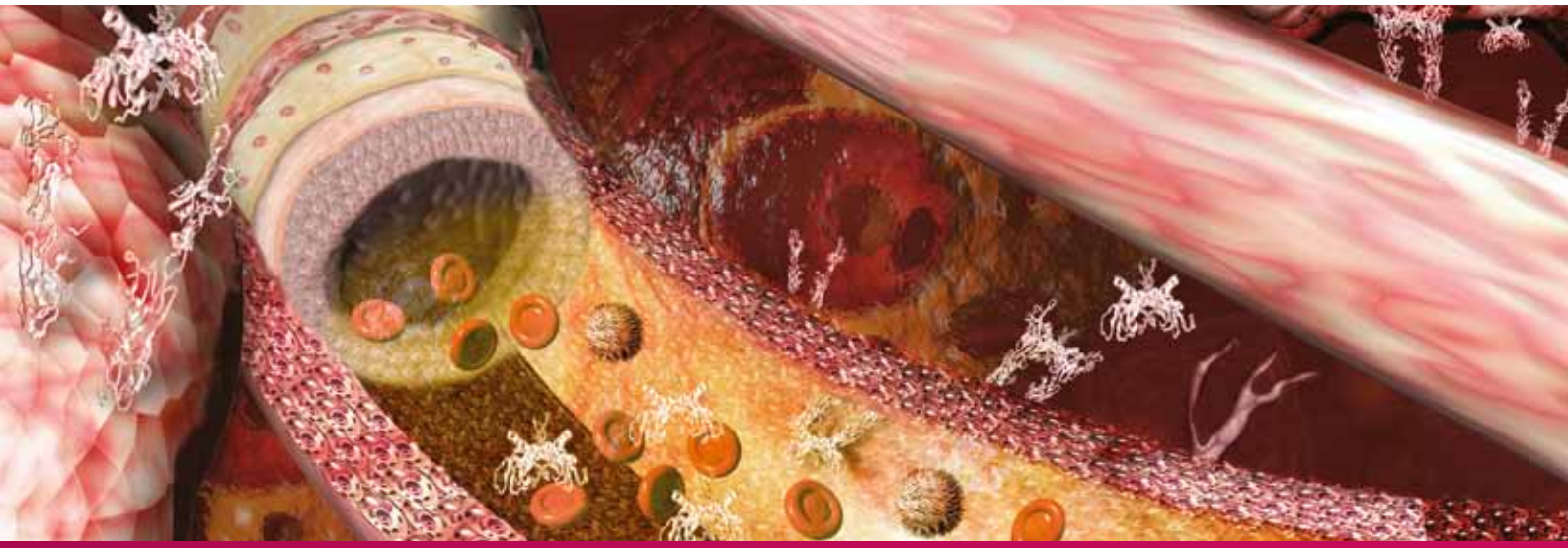

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colophon

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Belgian Journal of Hematology

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Volume 4, Issue 3, September 2013

Introduction

Dear Reader,

I hope you all enjoyed the summertime and had great holidays.

No lack of news during this summer: the last decennium, the world may have become small thanks to modern transportation and communication; but despite these progresses and possibilities, growing parts of our globe recently became out of reach for tourists. European countries where the economic crisis has struck hard are reaching out for visitors and their 'valuta'. Our colleagues in the regions of Spain, Portugal and Ireland try to deliver the same level of patient care and to go on with scientific research despite the decrease in financial support. For four Belgian scientists the burden of clinical responsibilities, academic duties and scientific output, was clearly unbearable. The scientific world reacted with words of understanding and a cry for change.

Above all, I'm convinced we should cherish our freedom and the opportunities still offered in this part of the world.

This edition of the BJH starts with a possibly underdiagnosed disorder: systemic mastocytosis. The subcommittee of the BHS working on lymphoproliferative diseases, delivered clear guidelines for the treatment of peripheral T-cell non-Hodgkin lymphomas, tailored in a well-written article. Ibrutinib is very probably one of the molecules in which the industry (financially) and the scientific community (medically) are placing their high hopes. As always we have a very intriguing case report, study protocol and thesis. We also have a nice contribution from people working in the field of non-malignant haematology, with facts on sickle cell anaemia, rounding off this issue of the BJH.

I'm sure there's something for every haematologist in the current BJH. Please keep sending us your contributions and any remarks for improvement are welcomed too.

I wish you enjoyable reading,

Dr Jan Van Droogenbroeck
Editor in chief

Systemic mastocytosis: overview and new insights in prognosis and therapy

G. Deslypere, MD[1], T. Devos, MD, PhD[2], M. Delforge, MD, PhD[2], G. Verhoef, MD, PhD[2]

Systemic mastocytosis is an orphan myeloproliferative disease characterised by an excessive mast cell accumulation. Benign forms present with urticaria pigmentosa while aggressive subtypes or leukaemic variants lead to organ dysfunction. In patients with unexplained hypotensive syncope's or anaphylaxis, flushing and angio-oedema with a basal tryptase >20 ng/mL, one should think of systemic mastocytosis. Pathophysiology is based on mutations in KIT, encoding the c-kit receptor (CD117) on the surface of mast cells. Diagnosis is based on bone marrow biopsies with clusters of atypical mast cells and co-expression of CD2 or CD25 and/or a KIT mutation. Treatment consists of avoiding triggers of mast cell release and antihistaminic drugs. Patients with aggressive subtypes are candidates for cytoreductive therapies. CD30 is thought to be a novel predictor of prognosis.

(Belg J Hematol 2013;4(3):85-89)

Introduction

Mastocytosis is a group of diseases characterised by an excessive mast cell accumulation in the skin and/or in the bone marrow or other solid organs.[1] Cutaneous mastocytosis patients present only with skin laesions, called urticaria pigmentosa or maculopapular cutaneous mastocytosis. Diffuse cutaneous infiltration of mast cells is less frequent and usually seen in children. The systemic variant presents with obligate bone marrow invasion and possible skin or other organ infiltration.[2] Mastocytosis is an orphan disease with unknown prevalence. Men and women are equally affected. In children the disease presents most often with only skin manifestations that can decrease or resolve in adulthood while adults present almost always with the systemic form. The systemic form cannot be cured and is very heterogeneous in presentation and prognosis. The disease is characterised by episodes of overwhelming mast cell degranulation, resembling an allergic or anaphylactic reaction and, in cases of aggressive variants, with organ dysfunction.[2]

Pathogenesis

The pathogenesis of systemic mastocytosis is not fully understood. It is known that in patients with systemic mastocytosis there is an excessive mast cell accumulation frequently associated with somatic activating point mutations in KIT encoding the c-kit receptor (CD117), a tyrosine kinase type III at the surface of the mast cells.[2,4,5] CD117 is important in the development and proliferation of mast cells. These special blood cells are the only hematopoietic cells not losing the expression of CD117 during maturation.[1] In >80% of patients with systemic mastocytosis this receptor has a gain of function mutation resulting in the stimulation of CD117 without the binding of stem cell factor (SCF). Nearly thirty KIT mutations have been described. The most commonly observed mutation shows substitution of Val for Asp at codon 816 (D816V) and is identified in the mast cells of 95% or more of adults with systemic mastocytosis when sensitive methods are used. These somatic mutations can be important for the development of specific treatments of systemic mastocytosis like

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

Key words: anaphylaxis, systemic mastocytosis, tyrosin kinase inhibitor.

Treatment of peripheral T-cell lymphomas: recommendations of the Belgian Hematological Society (BHS)

F. Van Obbergh, MD[1], A. Van Hoof, MD[2], G. Verhoef, MD, PhD[3], D. Dierickx, MD[3], V. De Wilde, MD, PhD[4], F. Offner, MD, PhD[5], D. Bron, MD, PhD[4], A. Sonet, MD[6], M. André, MD[6], A. Janssens, MD[3], C. Bonnet, MD, PhD[7], B. Deprijck, MD[7], P. Zachée, MD, PhD[8], A. Kentos, MD[9], W. Schroyens, MD, PhD[10], E. Van Den Neste, MD, PhD[1]

The sub-committee on lymphoproliferative disorders of the Belgian Hematological Society has met several times to prepare guidelines on the management of patients with peripheral T-cell lymphomas. Each panellist's expert provided interpretation of the evidence, based on literature review and personal experience. The available evidence was systematically discussed prior to formulating recommendations. A systematic approach to obtain consensus of expert opinion was used. After each meeting, the draft guideline was circulated to all experts for comment and approval. The present guidelines focus on general management of peripheral T-cell lymphomas with special emphasis on more specific disease-adapted strategies.
(Belg J Hematol 2013;4(3):90-101)

Diagnosis, classification, prognosis, fluorodeoxyglucose (FDG) avidity

T-cell lymphomas are divided into precursor T-cell (lymphoblastic) neoplasms, and mature post-thymic lymphomas. The latter are designated as peripheral T -cell lymphomas (PTCLs). PTCLs are highly diverse, reflecting the different cells from which they originate. These include cells from T-cell receptor (TCR) α/β, or TCRγ/lineages, and may have features of cytotoxic, helper, or suppressor lymphocytes, or may present with an aberrant phenotype. PTCLs also include neoplasms of natural killer (NK) cell origin because of the phenotypic and functional properties shared by some cytotoxic T cells and NK cells, with the fundamental difference being that the configuration of the TCR gene is germline in NK cell neoplasms. This is why, in the World Health Organization (WHO) classification of T-cell neoplasms, PTCLs are grouped under the designation "Mature T and NK cell neoplasms" (*Table 1*).[1]

The diagnosis of PTCL relies on a multiparametric methodology combining clinical, pathological, immunophenotypic, and genetic parameters. Detailing this complex approach is beyond the scope of the present recommendations. It is highly recommended to have the diagnosis reviewed by an experienced pathologist. Some entities are well defined, while others lack a distinct profile and are put into a wastepaper basket category called PTCL 'not otherwise specified' (NOS), in analogy of its B-cell counterpart diffuse large B-cell lymphoma (DLBCL), NOS. Because of the lack of dis-

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Key words: Non-Hodgkin lymphoma, NK-cell neoplasm, Peripheral T-cell lymphoma, T-cell neoplasm.

Ibrutinib: a major breakthrough in the treatment of chronic lymphocytic leukaemia (CLL) and other lymphoproliferative disorders

D. Bron, MD, PhD[1]

The Bruton's tyrosine kinase protein is expressed in most hematopoietic cells with the exception of T cells and natural killer cells, but the selective effect of Bruton's tyrosine kinase mutations suggests that its primary functional role is in antigen receptor signalling in B cells. Ibrutinib (=PCI-32765) was designed as a selective and irreversible inhibitor of the Bruton's tyrosine kinase protein. In vitro, PCI-32765 arrested cell growth and induced apoptosis in human B-cell lymphoma cell lines, and inhibited tumour growth in vivo in xenograft models. A first analysis performed on 116 naïve chronic lymphocytic leukaemia patients with a median age of 71 (range: 65 - 84) shows an estimated 22-months progression-free survival rate of 96%; the median progression-free survival or overall survival had not been reached.[1] In 61 patients with relapsed/refractory chronic lymphocytic leukaemia/small lymphocytic lymphoma with a median age of 64 years (range: 40 - 81) and a high-risk cohort (24 patients), the estimated 22-months progression-free survival rate for the 85 relapse/refractory and high-risk patients was 76%. PCI-32765 (ibrutinib) has demonstrated promising activity in studies enrolling older patients with treatment-naïve or relapsed/refractory chronic lymphocytic leukaemia and older patients with small lymphocytic lymphoma. Randomised phase III studies in naïve chronic lymphocytic leukaemia/small lymphocytic lymphoma patients are currently on-going.
(Belg J Hematol 2013;4(3):102-105)

Introduction

B cells are lymphocytes with multiple functions in the immune response, including antigen presentation, antibody production, and cytokine release. B cells express cell surface immunoglobulins that make up the B-cell receptor (BCR), which is activated by binding to antigen. Antigen binding induces receptor aggregation and the clustering and activation of multiple tyrosine kinases, which in turn activate further downstream signalling pathways.

The role of Bruton's tyrosine kinase (BTK) in BCR signal transduction is demonstrated by the human genetic immunodeficiency disease, X-linked agammaglobulinemia caused by a mutation in the BTK gene. These genetic diseases are characterised by reduced BCR signalling and a failure to generate mature B cells. The BTK protein is expressed in most hematopoietic cells with the exception of T cells and natural killer cells, but the selective effect of BTK mutations suggests that its primary functional role is in antigen receptor signalling in B cells.[2]

Summary of Pre-clinical Data

Ibrutinib (=PCI-32765) was designed as a selective and irreversible inhibitor of the BTK protein. In vitro, PCI-32765 (= Ibrutinib) is a potent inhibitor of BTK activity (half maximal inhibitor concentration ($[IC_{50}]$ = 0.5nM)). The irreversible binding of PCI-32765 to Cys-481 in

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

Key words: chronic lymphocytic leukaemia, kinase inhibitor, targeted therapy.

Myeloid sarcoma or lymphoblastic lymphoma? A closer look at the laboratory diagnosis

L. Roosens, PhD[1], K. Vermeulen, PhD[1], A. Verlinden, MD[2], H. Devos[3], E. Van Assche[3], I. Vrelust, MD[2], M-B. Maes, PhD[1], R. Malfait, MD[1]

Although a myeloid sarcoma is a rare form of extramedullary leukaemia, its early diagnosis has been proven to be of utmost importance. Its presence is strongly related to the onset or the presence of systemic bone marrow leukaemia. However, the diagnosis of myeloid sarcoma is not straightforward. In the existing literature, approximately half of the cases of myeloid sarcoma were initially misdiagnosed as lymphoma. The current case reports details on the laboratory diagnosis of myeloid sarcoma in a 25-year old male. The laboratory presentation of myeloid sarcoma and the consecutive steps in order to correctly diagnose myeloid sarcoma using a variety of laboratory techniques including microscopy, flow cytometry and cytogenetics are highlighted.
(Belg J Hematol 2013;4(3):106-109)

Introduction

A myeloid sarcoma (MS) has been defined by the World Health Organization (WHO) 2008 as a tumour mass consisting of myeloid blasts (granulocytes, monocytes or both) with or without maturation occurring at any anatomical site other than the bone marrow.[1] It is a rare condition which can occur in three clinical settings. Firstly, in non-leukaemic patients often preceding the onset of acute myeloid leukaemia (AML).[2] Secondly, associated with acute blast transformation of myelodysplastic syndrome (MDS) or chronic myeloid leukaemia (CML) and thirdly, in association with known AML.[3,4] Its diagnosis and treatment should be considered equivalent to that of AML and thus prognosis benefits from early detection. However, myeloid sarcomas are often misdiagnosed as malignant lymphomas. Literature reports up to 50% of misdiagnosed cases, especially in those patients presenting with primary MS.[5,6] The current case study reports a 25 year-old male presenting with a mediastinal mass, suggestive for lymphoblastic lymphoma, but due to adequate laboratory screening diagnosed as MS with bone marrow involvement.

Clinical presentation

A 25-year old male student had been complaining of a persistent cough for several months despite antibiotic treatment and was referred to the hospital by his doctor for a CT scan of the thorax. Upon arrival, the patient had an overall healthy appearance and did not report any serious medical history except a minor weight loss of about one kilogram, which was considered negligible.

Laboratory diagnostics

Full blood analysis was performed which did not reveal any abnormal parameters, including a perfectly normal blood cell count. The CT scan showed a large mediastinal mass which was further explored by PET scan and mediastinoscopy. A biopsy was taken. The age of the patient combined with his clinical presentation predicted the presence of a lymphoma. The screening procedure of the

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Key words: diagnosis, laboratory, myeloid sarcoma.

Current Clinical Trials

(Belg J Hematol 2013;4(3):111)

Protocol PCI-32765MCL3002: newly diagnosed mantle cell lymphoma

Sponsored by: Janssen Research and Development

BTK, ibrutinib, mantle cell lymphoma

This is a randomised, double-blind, placebo-controlled phase III study of Bruton's Tyrosine Kinase (BTK) inhibitor, PCI-32765 (ibrutinib), in combination with bendamustine and rituximab in subjects with newly diagnosed mantle cell lymphoma (MCL).

The primary objective of this study is to evaluate whether the addition of ibrutinib to bendamustine and rituximab will result in prolongation of progression-free survival (PFS) in subjects with newly diagnosed MCL who are 65 years of age or older. Approximately 520 subjects will be randomised in a 1:1 ratio and stratified by simplified mantle cell lymphoma international prognostic index. All subjects will receive open-label bendamustine-rituximab + blinded study drug (placebo versus ibrutinib) with rituximab maintenance every second cycle for a maximum of twelve additional doses.

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The effects of VEGFA/VEGFR interference on cell survival and angiogenesis in acute myeloid leukaemia: preclinical and clinical studies

A.C. Weidenaar, MD, PhD[1], A. ter Elst, PhD[1], W.A. Kamps, MD, PhD[1], E.S. de Bont, MD, PhD[1]

The research described in this thesis aimed to explore the various mechanisms by which vascular endothelial growth factor A promotes acute myeloid leukaemia progression via autocrine and/or paracrine mechanisms, e.g. angiogenesis. Special attention was focused on new potential small-molecule-inhibitors and antibodies interfering with vascular endothelial growth factor/vascular endothelial growth factor receptor signalling. We showed that interference with vascular endothelial growth factor A/vascular endothelial growth factor receptor signalling induces cell death in (paediatric) acute myeloid leukaemia blasts and primitive cells. Furthermore, we studied angiogenesis in bone marrow of acute myeloid leukaemia patients and identified different morphology patterns, related to treatment outcome.
(Belg J Hematol 2013;4(3):112-114)

Introduction

Acute myeloid leukaemia (AML) is a haematological disorder, characterised by disturbed differentiation of the myeloid lineage. Currently the main treatment for AML is chemotherapy. Although the outcome has improved over the last decades, over 40% of AML patients experience a relapse. Therefore, new therapeutic strategies are warranted.

In (paediatric) AML, cellular and circulating levels of vascular endothelial growth factor A (VEGFA) are elevated and adversely associated with prognosis.[1-3] Co-expression of VEGFA and its receptor tyrosine kinases (RTK) VEGF-Receptor-1 (VEGFR1) and VEGFR2 has been reported on AML cells, where VEGF/VEGFR signalling has proliferative effects.[4,5] Moreover, increased VEGFA levels are associated with higher micro vessel density in bone marrow (BM) of AML patients.[6,7] Together, these data suggest that targeting VEGF/VEGFR signalling might be an interesting therapeutic implication. Therefore, the aim of this thesis was to explore the various mechanisms of VEGFA on AML progression via autocrine and paracrine mechanisms, including angiogenesis.

Targeting leukaemia-initiating cells by VEGF/VEGFR interference

PTK787/ZK 222584 (PTK/ZK) is an RTK-inhibitor targeting VEGFR2 and VEGFR1, and to a lesser extent other RTKs (including VEGFR3, Platelet-Derived-Growth-Factor-Receptor-ß (PDGFRß), colony-stimulating-factor-1 receptor (CSF1-R) and c-KIT).[8] We showed that treatment with PTK/ZK induced cell death in AML cell lines and paediatric AML blasts in vitro.[9]

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

Key words: acute myeloid leukaemia, angiogenesis, vascular endothelial growth factor A.

News in sickle cell disease

A. Ferster, MD[1], B. Gulbis, MD, PHD[2]

During the twelfth meeting dedicated to sickle cell disease and hereditary red cell disorders held in Brussels on 21 February 2013, several topics related to major aspects for the management of sickle cell disease were presented. Six of them are summarised.
(Belg J Hematol 2013;4(3):115-116)

1. New-born screening for sickle cell disease in Brussels, a programme with an ongoing clinical outcome improvement.

The outcome of sickle cell disease (SCD) children diagnosed by newborn screening (NS) in the Brussels Region progressively implemented in 1994 and extended to all maternity wards in 2000, was reported by Lê et al (Department of Haematology and Oncology, Hôpital Universitaire des Enfants Reine Fabiola, Brussels, Université Libre de Bruxelles, Belgium). Children identified with SCD progressively benefited from comprehensive expert medical care in dedicated reference centres. Data from children born from January 1st 2000 to December 31st 2003 (group A) and from January 1st 2005 to December 31st 2008 (group B) followed, respectively, for 3.5 and 4.1 years, were compared. Compared to group A, children from group B had significantly fewer invasive infections, episodes of severe anaemia and acute chest syndromes whereas no significant difference was observed for dactylitis, vaso-occlusive crisis, clinical neurological event and for steady-state biological parameters. The conclusion of the authors is that, starting from newborn screening for sickle cell disease, progressive implementation of a comprehensive care has improved the outcome of patients over time.

2. Delayed haemolytic transfusion reaction (DHTR) in sickle cell disease.

Dr Noizat-Pirenne (Etablissement Français du Sang Ile de France et INSERM U955, Créteil, France) presented her experience and current knowledge on delayed haemolytic transfusion reaction (DHTR). DHTR is characterised by a marked haemoglobin drop, often below the pre-transfusion haemoglobin level, jaundice and haemoglobinuria developing several days post transfusion. It was described as a more frequent complication in SCD patients than in other patient populations. In DHTR, both transfused and autologous red blood cells are destructed; in SCD patients it is accompanied by exacerbation of the pain mimicking a vaso-occlusive crisis. Further transfusion generally worsens the haemolytic process. Additionally, the patho-physiological role of allo-antibodies, but also of auto-antibodies and non-immunological haemolysis is argued. These latter phenomena could be explained by previous modification of the red cell membrane, e.g. surface exposition of phosphatidylserine, in the context of a systemic inflammation, as it is usually present in SCD patients. DHTR is often underestimated but its risk should alter clinicians conduct to restrict transfusions, especially in the case of well tolerated anaemia or uncomplicated vaso-occlusive crisis.

3. Cerebral revascularisation and moyamoya in sickle cell disease.

Due to cerebral vasculopathy affecting large cerebral arteries, eleven percent of SCD children develop neurological events before the age of 20. In addition to this large vessel arteriopathy, moyamoya will develop in 40% of children, hampering their prognosis despite correct chronic transfusion management. Dr Blauwblomme

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Key words: sickle cell disease.

International & national congresses 2013

October 4-6	**ESH International Conference on Multiple Myeloma** Dublin, Ireland For more information please visit: http://www.esh.org/conferences/
October 24-27	**ESH / Eurocord-Ed / Eurocord World Cord Blood Congress IV and Innovative Therapies for Sickle Cell Disease** Monaco, Principality of Monaco For more information please visit: http://www.esh.org/conferences/
November 6-7	**ESH International conference on haematological disorders in the elderly** Barcelona, Spain For more information please visit: http://www.esh.org/conferences/
November 7-9	**Markers in Cancer (A joint meeting by ASCO, EORTC and NCI)** Brussels, Belgium For more information please visit: http://www.markersincancer.eu/
November 12-14	**13th ESCCA Euroconference on Clinical Cell Analysis** Luxembourg, Luxembourg For more information please visit: www.escca.eu/lux2013/
November 14	**5th Amsterdam Symposium Haematology - IKNL** Amsterdam, The Netherlands For more information please visit: http://www.iknl.nl/Amsterdam/werkgroepen/hemato_oncologie/index.php?id=6453
November 15-16	**9th ESCCA European Course on Clinical Cytometry** Luxembourg, Luxembourg For more information please visit: www.escca.eu/lux2013/
November 17	**Hovon protocol days** Amersfoort, The Netherlands For more information please visit: http://www.hovon.nl/
December 1-4	**24th Regional Congress of the International Society of Blood Transfusion (ISBT)** Kuala Lumpur, Malaysia For more information please visit: http://www.isbtweb.org/
December 7-10	**55th ASH Annual Meeting and Exposition** New Orleans, USA For more information please visit: http://hematology.org/Meetings/Annual-Meeting/
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