BSTH
Belgian Society on Thrombosis and Haemostasis

Belgian Journal of Hematology

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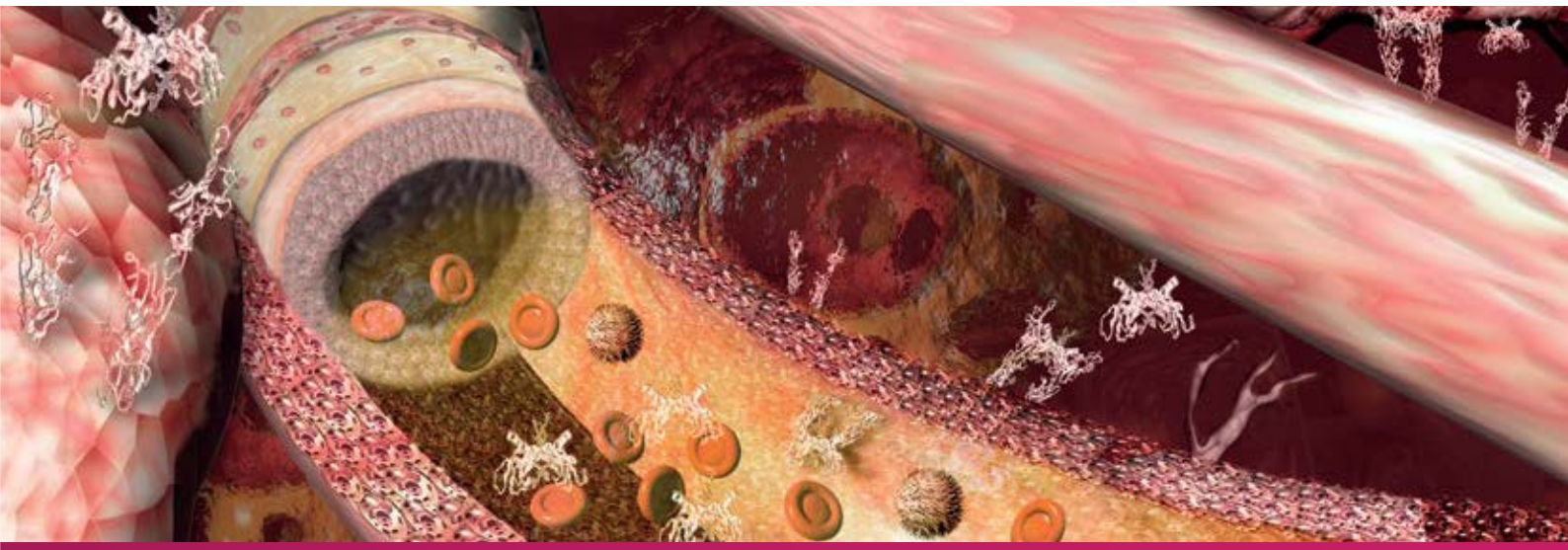
Belgian Hematological Society

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)

Volume 4, Issue 1, March 2013



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colophon

The Belgian Journal of Hematology (BJH) 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).
The 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 haematological 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 1, March 2013

Introduction

Dear Reader,

This issue of the BJH is an example of what we wanted to achieve with the launch of this Journal almost 3 years ago.

The first article covers an intriguing and completely novel field in hematology/oncology, summarising the topic of microvesicles in cancer. Furthermore the authors are Belgian and at the forefront of this new and thus controversial area of research. As it's a controversial topic, the board thought it wise to add an editorial, but I do hope our readers can appreciate topics off the beaten track.

The (Belgian) guidelines for diagnosis and treatment of idiopathic thrombocytopenic purpura will be of interest for the starting hematologist and expert alike. It gives clear answers to several relevant clinical questions when confronted with a patient with ITP.

The article on immunomodulatory drugs covers new and promising terrain within our treatment options for different hematological malignancies.

In addition, the hematotrial describes a trial that will study if combining a moclonal antibody with immunomodulatory drugs (lenalidomide) could be non inferior to our classical approach with the same monoclonal and conventional chemotherapy, in treating follicular Non Hodgkin lymphoma.

As in every issue of the BJH, the hematocase is a well-written eye-opener.

Last but not least, the "Best of ASH 2012" cannot be forgotten in the first issue of 2013.

I wish you all enjoyable reading,

Jan Van Droogenbroeck, MD, PhD
Editor in chief

Microvesicles and cancer

M-A. Azerad, F. Debaugnies, A. Demulder, D. Bron, A. Efira

Microvesicles (MV) are since quite recently recognized as forming a unique network between cells. These very little fragments (<1 µm size) are actively released from their parent cells and are able to transfer both cellular and nuclear material. Although active debate remains on how to best detect MV, rendering some results questionable, high MV levels have been reported in aggressive tumours and have been correlated with a poor clinical outcome. Some tumour cell derived MV exhibit strong tissue factor dependent procoagulant activity. Their detection could actually predict the thrombotic risk in selected cancer patients. A growing body of evidence suggests cell microvesicles to be a major link between cancer and thrombosis. Current knowledge on MV in cancer will be reviewed here.
(Belg J Hematol 2013;1:3-8)

Introduction

There is active debate in the literature on a definition of microparticles (MP) and microvesicles (MV). The basic mechanism of MP formation is disruption of the machinery supporting asymmetry of phospholipids between the two layers of the membrane. Platelet-derived microparticles (PMP) constitute the majority of the pool of MP circulating in the blood. Besides cancer, high levels of MP have been demonstrated in inflammatory diseases, renal insufficiency, diabetes, heart diseases.[1]

Current definition of MP is based on size parameters: small plasma membrane vesicles (<1 μm) shed from the outer membrane of the cells upon their activation or apoptosis.[1] They carry the epitopes of the cells they are issued from.

Exosomes are smaller microvesicles (30-80nm) which can also be actively released and contain both cellular and nuclear material. Exosomes are formed within endosomal structures, then released and exhibit different markers as compared to MP. Although this classification based on the different origin (intracytoplasmic bodies) and molecular content is obvious for many authors, others consider that the distinction between MP and exosomes is probably not justified since the same mechanism of active transfer of materials does exist for both types of structures.[2,3] MV act indeed as a real network and allow at a nano-level a highly potent communication system between cells.[4]

Cancer has long been associated with thrombosis. MP have been shown to carry Tissue Factor (TF) which can be activated at the site of vascular injury or bind to activated platelets initiating then locally thrombin generation, thereby activating coagulation.[5]

Tesselaer et al in 2007 published a revolutionary paper stating that they found the 'missing link between thrombosis and cancer'.[6]

Other papers have confirmed that elevated levels of MP can be found in different tumour types: glioblastomas, prostate, pancreas, colon, head and neck and breast cancer, high levels have been associated with a poor prognosis.[3]

As shown in *figure 1,* MV can facilitate cancer progression via different pathways.

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

Key words: Microvesicles, microparticles, cancer, hypercoagulability, tissue factor, thrombin generation.

How to isolate and analyse microvesicles in human samples?

Editorial for the contribution of M-A. Azerad et al, entitled: Microvesicles and cancer

F. Mullier, N. Bailly, C. Chatelain, B. Chatelain, J-M. Dogné

(Belg J Hematol 2013;1:9-10)

In this edition of the Belgian Journal of Hematology, Azerad et al. discuss the definition, analysis and roles of microparticles/microvesicles (MVs) in cancer. Microvesicles are small spherical structures highly heterogenous both in size and in composition.[1,2] As stated by Azerad, the MV nomenclature is still a matter of debate since there is no consensus on size distribution due to inaccuracy and imprecision of size measurement.[1,3] As potential disease biomarkers, MV measurement and characterisation in biological fluids could reveal new diagnostic and/or prognostic information in human diseases.[4,5] Currently, the detection and quantification of MVs are hampered by their methods of isolation and their nanometric size.[6-8] Therefore, the validation and standardisation of sensitive characterisation techniques are needed. This is challenging since a wide range of pre-analytical variables including blood sampling, sample handling, plasma generation, and plasma freezing/storing are considered as major sources of variability and potential artefacts in MV analysis. Briefly, after gentle transport, 109mM citrated whole blood should be centrifuged at room temperature within 30min to 1h to isolate plasma, with a light brake only. A double centrifugation step at 2,500g is recommended to ensure removal of platelets and decrease platelet MV production during subsequent freeze/thawing. Samples processed fresh and those frozen prior to analysis should not be directly compared. In addition, frozen-thawed plasma should ideally be stored for an equal length of time and no more than one year. This information is often lacking and should be clearly highlighted.[9-11]

As indicated by Azerad., no 'gold standard' technique is recognized so far to characterize MVs. Each method has specific advantages and drawbacks. Inter-laboratory comparisons are currently not possible due to absence of appropriate biological MV preparations ('calibrators') with well defined characteristics (i.e. size distribution, concentration). Flow cytometry (FCM) remains the technique most used to quantify MVs and give insight into the cellular origin. FCM suffers from a lack of sensitivity for small size MVs (size<500nm) although recent improvements provided access to previously undetectable MVs (lower size limit: 200-300nm).[12] It is unknown if looking at smaller MVs will give additional biological information.[13] Submicron polystyrene beads are interesting tools in FCM to help in qualifying instruments and measure a reproducible part of the largest MVs.[14] However, absolute sizing of MVs using scatter parameters and polystyrene beads also presents drawbacks.[15-17] Interestingly, the use of specific protocols

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

Primary immune thrombocytopenia in adults

Guidelines for diagnosis and treatment anno 2013 proposed by the Belgian Hematological Society

A. Janssens, C. Lambert, G. Bries, A. Bosly, D. Selleslag, Y. Beguin

The Belgian Hematological Society (BHS) guideline panel on adult primary immune thrombocytopenia (ITP) reviewed the recent literature on diagnosis and treatment to make recommendations on the best strategies for frontline and subsequent-line treatment. No treatment is necessary for patients with platelet counts higher than 30000/µl in the absence of bleeding symptoms. Patients newly diagnosed or relapsing after a long-term treatment-free period can be managed with corticosteroids with or without intravenous immunoglobulins. A second line therapy is indicated for those patients who are intolerant or unresponsive to or relapse after initial corticosteroid treatment and have a risk of bleeding. The guideline panel recommends splenectomy as it is the treatment with the highest curative potential and an acceptable safety profile. If possible, splenectomy should be delayed to at least twelve months after diagnosis as spontaneous remission can occur in this time period. Thrombopoietin receptor (TPO-R) agonists are recommended for patients who are refractory to or relapse after splenectomy or who have a contra-indication to splenectomy irrespective of the duration of ITP. The guideline panel agrees that rituximab, azathioprine, cyclophosphamide, cyclosporine A, danazol, dapsone, mycophenolate mofetil and vincristine/vinblastine are potential treatment options, especially for patients refractory to TPO-R agonists.

(Belg J Hematol 2013;1:11-20)

Introduction with definitions

Immune thrombocytopenia is an acquired autoimmune disease characterised by an isolated low platelet count number (<100,000/µl). The disorder is classified as primary immune thrombocytopenia (ITP) in the absence of any obvious initiating and/or underlying cause, and as secondary ITP in association with autoimmune disorders (systemic lupus erythematosus (SLE), the antiphospholipid syndrome (APS), etc.), some immunodeficiency syndromes (CVID, adult lymphoproliferative syndrome, etc.), lymphoproliferative disorders (chronic lymphocytic

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

Key words: primary immune thrombocytopenia, treatment, corticosteroids, intravenous immunoglobulins, thrombopoietin receptor agonists, rituximab.

Immunomodulatory drugs: new developments

K. Fostier, A. De Becker, R. Schots

The immunomodulatory drugs (IMiDs) are a class of orally available compounds which are licensed for the treatment of multiple myeloma (thalidomide, lenalidomide) and transfusion-dependent low- and intermediate-risk myelodysplasia (MDS) with deletion of long arm of chromosome 5 (lenalidomide). Pomalidomide, a novel second generation IMiD, is entering clinical trials and seems to further broaden the therapeutic spectrum of these already pleiotropic drugs. Here we summarise new insights into the mechanism of action of IMiDs as well as new developments related to their clinical use, as maintenance therapy in multiple myeloma (MM), in the treatment of myeloproliferative neoplasm- associated myelofibrosis, other types of MDS, chronic lymphocytic leukaemia (CLL) and sickle cell disease (SCD).

(Belg J Hematol 2013;1:21-28)

Introduction

Thalidomide (Thal), the parent drug of all immunomodulatory drugs (IMiDs) was synthesised in 1954 in Germany and sold initially as an over the counter drug with sedative properties. However, Thal proved to be teratogenic and the phocomelia disaster in the late fifties led to its withdrawal from the market in 1961. Nevertheless, interest in Thal remained because of its activity in erythema nodosum leprosum (a reactive state in lepromatous leprosy), its ability to reduce TNF-alpha production by activated human monocytes as well as intrinsic immunomodulatory and anti-angiogenic properties. Further studies led to the development of second generation IMiDs, lenalidomide (Len) and pomalidomide (Pom), which are structurally closely related to Thal.

New insights in the mechanism of action

Second generation IMiDs are approximately 50,000 times more potent than the parent compound at TNF-alpha inhibition but also exert the capacity to costimulate T-cells. They also diminish the secretion of prostaglandin PGE2 and inhibit cyclo-oxygenase 2. IMiDs also intervene at many crossroads in the innate and adaptive immune system. They promote formation of NK lymphocytes, augment antibody dependent cell mediated cytotoxicity, promote expression of FAS-ligand, drive the expansion of NKT cells and their interferon gamma production and skew the immune system towards a Th-1 response. In contrast, Len and Pom inhibit proliferation and function of regulatory T cells. Thal inhibits neo-vascularisation in in vitro assays and in murine models of human tumours, irrespective of its immunological effect. Len and Pom exhibit to a lesser extent anti-

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

Key words: Thalidomide, lenalidomide, pomalidomide, IMiD, myelofibrosis, myelodysplasia, chronic lymphocytic leukaemia, maintenance therapy, myeloma.

Pregnancy-Related Thrombotic Microangiopathy (TMA): Case series

B. Al-Atia, T. Devos, G. Verhoef, D. Dierickx

Thrombotic microangiopathy (TMA) can be a key feature of several pregnancy related disorders such as thrombotic thrombocytopenic purpura (TTP) / Haemolytic uremic syndrome (HUS), congenital TTP(CTTP), HELLP syndrome, or acute fatty liver (AFL). TMA is a life threatening condition in pregnancy. It encompasses a spectrum of different disorders with a similar pathogenesis, but in most of the cases completely different therapy. It can take several days to obtain the diagnosis, and in case of doubt therapeutic plasma exchange (TPE) (plasmapheresis with plasma substitution) should be started immediately to ensure better outcome. By measuring the activity of the von Willebrand-factor-cleaving protease (ADAMTS13), it may be possible to distinguish between the different causes of thrombotic microangiopathy. Pregnancy-related TMA can occur before or after birth. A Pregnancy-related TMA that develops during the puerperium, typically develops about the fourth day postpartum. No other significant differences are seen between antepartum and postpartum pregnancy related TMA. In critically ill patients it may be difficult to distinguish TMA from sepsis with disseminated intravascular coagulation (DIC). DIC is generally associated with prolongation of global clotting times, prothrombin time and activated partial thromboplastin time (PTT, aPTT) due to consumption of clotting factors. TMA occurs by primary activation of platelets (congenital or acquired abnormalities of ADAMTS13), and by primary endothelial injury (as with HELLP syndrome). Antepartum pregnancy-related TMA usually occurs at 28 ± 8 weeks of pregnancy.

(Belg J Hematol 2013;1:29-35)

Introduction

In this paper we describe a case series of five women presenting with pregnancy-related TMA. We emphasise that correct diagnosis is essential for correct management, and for optimal maternal and fetal outcomes. The patients described here developed thrombotic microangiopathy with a different etiology, despite every similar symptoms.

Clinical description of the cases, with theoretical aspects

Case 1: Idiopathic TTP

A 30 year-old woman was admitted to the gynecological department for urgent labor because she developed clinical manifestations of preeclampsia/HELLP at the gestational age of 28 weeks. Two days after delivery, she developed acute neurological features,

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

Key words: Thrombotic microangiopathy (TMA), thrombotic thrombocytopenic purpura (TTP), haemolytic uremic syndrome (HUS), congenital TTP (CTTP), HELLP syndrome: H (haemolysis, which is the breaking down of red blood cells), EL (elevated liver enzymes), LP (low platelet count), ADAMTS 13 (A disintegrin and metalloprotease with Thrombo-Spondin 1 repeats, 13th member), disseminated intravascular coagulation (DIC), acute fatty liver (AFL), therapeutic plasma exchange (TPE).

RELEVANCE: A phase 3 randomised study comparing efficacy and safety of rituximab plus lenalidomide versus rituximab plus chemotherapy in first-line patients with follicular lymphomat

M. André

(Belg J Hematol 2013;1:36-38)

1. Objectives of the trial

The primary objective of the study is to compare the efficacy of rituximab plus lenalidomide to rituximab plus chemotherapy followed by rituximab in patients with previously untreated follicular lymphoma. Efficacy determination will be based upon the co-primary endpoints of complete response (CR/CRu) rate at 120 weeks and PFS assessed by the IRC using the IWG criteria.

The secondary objectives of the study are:

1. To compare the efficacy of rituximab plus lenalidomide versus rituximab plus chemotherapy followed by rituximab using other parameters of efficacy.
2. Time to Treatment Failure (TTF), Event Free Survival (EFS), Time to Next Anti-Lymphoma Treatment (TTNLT), Time to Next Chemotherapy Treatment (TTNCT), Overall Survival (OS) and ORR rate at 120 weeks by IWG 1999 criteria.
3. Health related quality of life as measured by the EORTC QLQ- C30.
4. To compare the safety of rituximab plus lenalidomide versus rituximab plus chemotherapy followed by rituximab.

2. Research plan and methods

2.1 Major inclusion criteria

- Histologically confirmed CD20+ follicular lymphoma grade 1, 2 or 3a as assessed by the investigators.
- Have no prior systemic treatment for lymphoma.
- Must be in need of treatment as evidenced by at least one of the following criteria:
  1. Bulky disease defined as: 1) a nodal or extra nodal (except spleen) mass >7cm in its greater diameter or, 2) involvement of at least three nodal or extra nodal sites (each with a diameter greater than >3 cm).
  2. Presence of B symptoms.
  3. Symptomatic splenomegaly.
  4. Compression syndrome (ureteral, orbital, gastrointestinal).
  5. Any one of the following cytopenias due to lymphoma: 1) hemoglobin <10g/dL (6.25 mmol/L) 2) platelets <100 x 109/L, or 3) absolute neutrophil count (ANC) <1.5 x 109/L.

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

Key words: follicular lymphoma, rituximab, lenalidomide

International & national congresses

April 6-10, 2013	**AACR Annual Meeting** Washington DC, USA. For more information please visit: http://www.aacr.org/home/scientists/meetings--workshops/aacr-annual-meeting-2013.aspx
April 7-10	**39th EBMT Annual Meeting** London, UK. For more information please visit: http://www.ebmt.org/Contents/Annual-Meeting/39thEBMTAnnualMeetingin2013/Pages/38th-EBMT-Annual-Meeting-in-2012.aspx
April 18-19	**14th Annual NATA Symposium** Vienna, Austria. For more information please visit: http://www.nataonline.com/node/41
April 24-27	**26th Annual ASPHO Meeting** Miami, FL, USA. For more information please visit: http://www.aspho.org/education/content/meeting.html
April 25-27	**Second ESH-EHA Scientific Workshop on Leukemic and Cancer stem cells: malignant stem cells and their microenvironment** Mandelieu, France. For more information please visit: http://www.esh.org/conferences/
April 25-28	**17th ESH - EBMT Training Course on Haemopoietic Stem Cell Transplantation** Syracuse, Italy. For more information please visit: http://www.esh.org/conferences/
May 8-11	**12th International Symposium on Myelodysplastic Syndromes** Berlin, Germany. For more information please visit: http://www2.kenes.com/MDS/INFO/Pages/WelcomeLetter.aspx
May 10-12	**26th International Symposium on Technological Innovations in Laboratory Hematology (ISLH)** Toronto, Canada. For more information please visit: http://www.islh.org/ISLH_2013/index.php?page
May 20-24	**International Society of Hematology (ISH)** La Habana, Cuba. For more information please visit: http://www.ishworld.org/
May 31-June 4	**ASCO Annual Meeting** Chicago, IL, USA. For more information please visit: http://chicago2013.asco.org/
June 2-5	**23rd Regional Congress of the ISBT** Amsterdam, The Netherlands. For more information please visit: http://www.isbtweb.org/
June 13-16	**18th Congress of EHA** Stockholm, Sweden. For more information please visit: http://www.ehaweb.org/congress-and-events/18th-congress/key-information/
June 29-July 4	**24th ISTH Congress with 59th Annual SSC Meeting** Amsterdam, The Netherlands. For more information please visit: http://www.isth2013.org/

Erratum

In the supplement of the BHS General Annual Meeting, the co-authors of abstract O.8 were missing. Please find them listed below:

"The value of asparaginase intensification for children with low and average risk acute lymphoblastic leukaemia (ALL) and non-Hodgkin Lymphoma (NHL) in the EORTC-CLG Randomized Phase III Trial 58951".

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