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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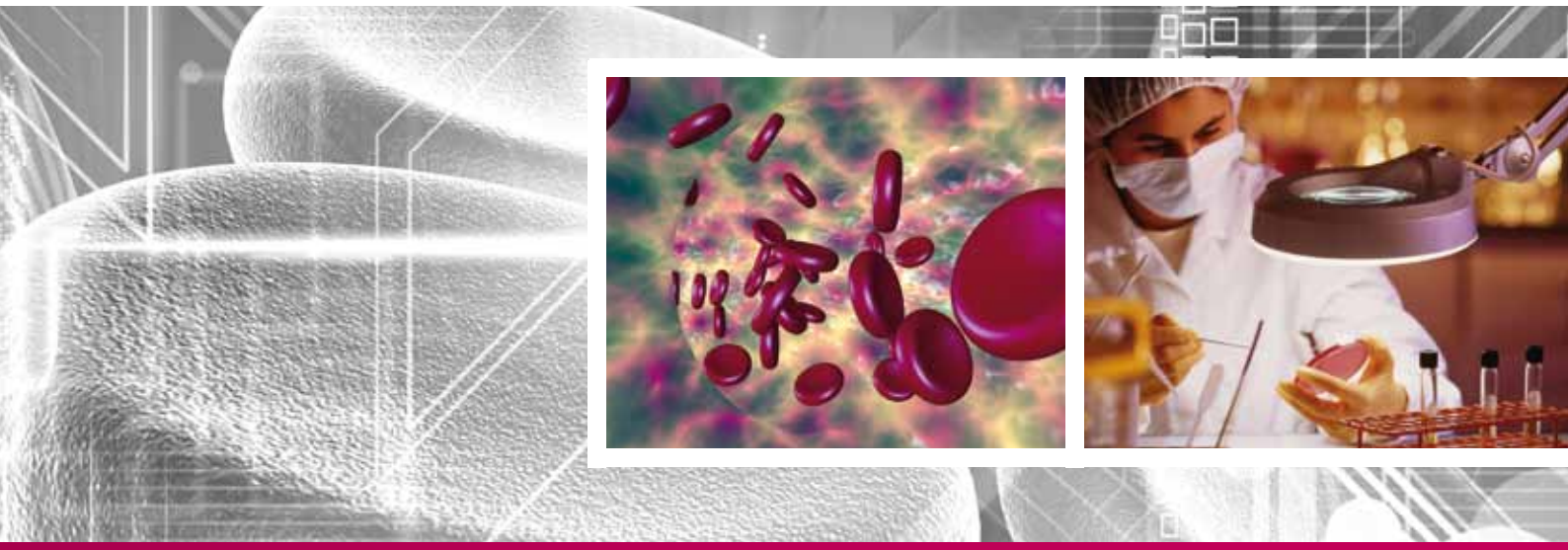

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colophon

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Volume 3, Issue 3, September 2012

Introduction

Dear Reader,

I hope every one of you had a great summer and enjoyed rejuvenating holidays. With the arrival of autumn, the third issue of the BJH has been dropped in your post-box.

The topics covered in this journal span - again - a broad spectrum. The transplant physicians will read a nice review article on haploidentical stem cell transplantation and a summary of the EBMT meeting held earlier this year in Geneva.

There's much to do about the new anticoagulants and their cost-effectiveness; Prof. S. Simoens was willing to write an overview on this interesting but difficult subject.

We have a (well studied) point of view about the new guidelines on ESAs by Dr. L. Plawny. Dr. K. Fostier and Prof. R. Schots sent in a nice article on proteasome inhibition in myeloma and some other haematological malignancies.

The hematocase is intriguing and brought to you by a group of experts in clinical and laboratory haematology.

Dr. D. Dierickx presents an international phase II trial in PTLD.

Finally, I would especially like to thank Dr. T. Lodewyck, Prof. A. Bosly, Prof. J. F. Baurain and Dr. W. Lybaert, for their contributions on international meetings they attended and covered for this journal.

I wish you enjoyable reading,

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

Haploidentical stem cell transplantation in adults: novel strategies and future directions

D. Selleslag

Haploidentical stem cell transplantation is an attractive form of alternative donor transplantation because of the immediate donor availability, ease of stem cell procurement, and the possibility to collect donor cells for further cellular therapy. T-cell depleted haploidentical transplantation (the Perugia approach) has been limited by a high nonrelapse mortality related to infectious complications as a result of delayed immune reconstitution posttransplantation. Research in this field is focusing on improving immune reconstitution by immunotherapy with different types of T-cells that do not cause graft-versus-host disease. A more recent modality (Hopkins approach), resulting in a decreased risk of graft-versus-host disease, is the use of T-cell replete haploidentical stem cells in combination with posttransplantation high-dose cyclophosphamide to eliminate expanding alloreactive T-cells. Research with this approach is focusing on the prevention of disease relapse posttransplantation. It seems that the most important barriers against successful haploidentical transplantation can now be overcome. This review evaluates the opposing modalities (T-cell replete versus T-cell depleted approach) and future directions of haploidentical stem cell transplantation in adults.

(Belg J Hematol 2012;3:74-81)

Introduction

Hematopoietic stem cell transplantation (HSCT) offers a curative treatment for many patients with malignant and nonmalignant haematological disorders. As the probability of finding an HLA-identical sibling donor is only 25-30%, attention has been focused on the use of alternative donor sources either from unrelated donors, umbilical cord blood or partially matched related donors. The chance of finding a matched unrelated donor varies from 60-70% for Caucasians to less than 10% for ethnic minorities.[1,2] Further drawbacks for a patient who urgently needs a HSCT are the time interval from initiating an unrelated donor search to the identification of an appropriate donor (currently about 4 months) and the considerable costs of high resolution typing.[3] Unrelated cord blood has become a new promising stem cell source due to its faster availability, tolerance of HLA-mismatching, lower incidence and severity of graft-versus-host disease (GVHD) and lack of risk for the donor. However, the limited unit size, slow hematopoietic and immune recovery and high incidence of transplant infections are obstacles to its broader application especially in adult patients. These limitations have been partially overcome by infusing two umbilical cord blood units, which improved engraftment and disease free survival.[4]

Haploidentical HSCT has been developed to address limitations in donor availability. Virtually all patients have a one haplotype mismatched family donor.

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

Keywords: Haploidentical stem cell transplantation, T-cell depletion, CD34 selection, immune reconstitution, NK-cell alloreactivity.

Cost-effectiveness of anticoagulants

S. Simoens

Anticoagulants reduce blood clotting and are effective in preventing and treating venous thromboembolism, stroke and myocardial infarction. New oral agents such as dabigatran and rivaroxaban have recently been approved for these indications. Dabigatran and rivaroxaban benefit from oral administration, but have a higher potential for drug interactions than low molecular weight heparins. As compared with warfarin, dabigatran and rivaroxaban have a rapid onset of action and a predictable anticoagulant effect, obviating the need for routine coagulation monitoring. Although there are few economic evaluations of anticoagulants, the existing evidence suggests that the cost-effectiveness of anticoagulants depends on the alternative with which the anticoagulant is compared and on the specific disease.
(Belg J Hematol 2012;3:82-87)

Introduction

Anticoagulants reduce blood clotting and are effective in preventing and treating venous thromboembolism (which includes deep venous thrombosis and pulmonary embolism), stroke and myocardial infarction. For instance, anticoagulants reduce the risk of stroke by 67% to 80%.[1] These diseases are not only a leading cause of morbidity and mortality in the developed world, but also impose an economic burden on society in terms of health care costs and productivity loss. For instance, the mortality rate associated with pulmonary embolism is 13% in elderly patients one month after onset, rising to 17.5% within three months.[2] The total annual health care costs (excluding physician costs) of venous thromboembolism have been estimated at US$1.5 billion in the United States, 70% of which are generated by hospitalisation.[3]

Health economic evaluation is an instrument that assesses the cost-effectiveness of a medicine as compared with an alternative. Evidence derived from economic evaluations is used to inform pharmaceutical reimbursement (and/or pricing) decisions in many countries. The requirement for economic evaluation fits within an overall trend towards evidence-based decision making in health care.

The results of an economic evaluation can be expressed in the form of an incremental cost-effectiveness ratio. This ratio relates the difference in costs between a medicine and the comparator to the difference in outcomes. The incremental cost-effectiveness ratio is then compared with a threshold value, which reflects the maximum cost per unit of outcome that a health care payer is willing to pay for a medicine. For instance, the National Institute for Health and Clinical Excellence (NICE) in England and Wales uses a threshold value of £20,000 - £30,000 per quality-adjusted life year (an outcome measure taking into account life expectancy and quality of life). A medicine with an incremental cost-effectiveness ratio below the threshold value is likely to be accepted by a health care payer and a medicine with a ratio exceeding the threshold value is likely to be refused.

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Conflict of interest: S. Simoens has acted as a consultant to Bayer Pharma on rivaroxaban.

Keywords: Cost-effectiveness, anticoagulants, venous thromboembolism, stroke, myocardial infarction.

Point of view about new guidelines on ESAs (erythropoiesis-stimulating agents)

L. Plawny

Recent concerns about the safety of erythropoietin stimulating agents (ESAs) in cancer patients have led to a reformulation of the guidelines issued by NCCN, ASH/ASCO and ESMO. The goal of this review is to comment on various safety issues like mortality or thromboembolism or iron supplementation and to summarise the views of the three working groups concerning ESA treatment in cancer patients.

(Belg J Hematol 2012;3:88-94)

Introduction

Anaemia, defined by a haemoglobin level below 14 g/dl in men and below 12 g/dl in women is a frequent finding in cancer patients and can be subdivided into mild (Hb >10g/dl), moderate (Hb 8-10 g/dl), severe (<8g/dl) and life threatening anaemia.[1] Cancer may suppress erythropoiesis either directly by bone marrow invasion or indirectly by producing TNF-alpha and other cytokines which reduce EPO production. TNF-alpha mediated dysregulation of the GATA1/GATA2 pathways whose expression may either lead to erythrocyte differentiation or suppression of normal erythropoiesis is also thought to contribute to cancer-related anaemia.[2,3] Concurrently cancer is accompanied by various clinical states contributing to the pathogenesis of anaemia like infection denutrition or renal insufficiency.[4,5,6]

Anaemia has been recognised as an adverse prognostic factor and the management of anaemia positively affects quality of life in cancer patients.[4,5,6]

The use of erythropoiesis stimulating agents (ESAs) in cancer related anaemia was a widely used and commonly accepted treatment option in the beginning of the 2000s. At that time however first studies demonstrated an increase in mortality in cancer patients undergoing ESA therapy.[7,8] Moreover, the same studies indicated that patients whose anaemia was treated with erythropoietin were prone to venous thromboembolism. Moreover, preclinical data concerning the presence of erythropoietin receptors on tumour cells and a clinical study on head and neck cancer patients displaying reduced disease free survival in patients treated with ESA therapy raised the question of tumour progression under ESA therapy.[9,10] These concerns have led to a reformulation of the guidelines issued by ESMO, NCCN, ASH/ASCO and had a negative impact on the prescription of ESAS.[11,12] FDA initiated a risk evaluation and mitigation strategy program in which all patients receiving ESA therapy must be included prior to undergoing treatment.[4]

The goal of this review is to provide the clinician with a commented summary of current guidelines.

1. Assessment of anaemia

When faced to a cancer patient displaying anaemia, the clinician should keep in mind that cancer- or chemotherapy-induced anaemia remains an exclusion diagnosis and that the patient should be checked for any other cause of anaemia related or not to cancer,

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

Keywords: Erythropoietin, cancer.

Proteasome inhibitors in multiple myeloma and other haematological malignancies

K. Fostier, R. Schots

The proteasome is an important anticancer target. Bortezomib, as a first-in-class proteasome inhibitor has become a valuable drug in the therapeutic armamentarium against multiple myeloma. This drug-review summarises the current indications for the use of bortezomib in myeloma. In addition, its emerging role as a consolidating / maintenance agent after autologous stem cell transplantation and its use in patients with bad cytogenetical markers or renal impairment is addressed. We also include the available data on the subcutaneous route of administration as an alternative to mitigate peripheral neuropathy. The promising evidence of proteasome inhibitors in other haematological malignancies (low grade lymphomas, mantle cell lymphoma, Waldenström's disease and systemic amyloidosis) is also summarised.
(Belg J Hematol 2012;3:95-104)

Introduction

Bortezomib (Velcade®), a boronate peptide, is the first-in-class of a clinically usable proteasome inhibitor. Although initially conceived in the nineties as a drug to reduce the excessive proteolysis that causes muscle wasting and cachexia, the drug has become part of the standard of care of newly diagnosed and relapsed multiple myeloma (MM). Nevertheless, there are several shortcomings to the molecule, such as the reversibility of the proteasome inhibition, the neuropathy, the parental route of administration and the emergence of drug resistance.

1. Mechanism of action

The ubiquitin-proteasome pathway is a major protein degradation system for intracellular proteins. The proteasome not only degrades misfolded or damaged proteins, but also many cell-cycle control factors (cyclins and cyclin-dependent kinase inhibitors), transcription factors, oncogenes and tumour suppressor proteins (e.g. p53).[1,2] Hence, the proteasome is a main regulatory switch of cell proliferation, differentiation, and apoptosis. Proteasome inhibition in MM leads to a multitude of biological effects *(Figure 1)*.[3] Bortezomib not only targets the myeloma plasma cell but also the stromal bone marrow cells, osteoblasts and osteoclasts. One of the most cited targeted pathways of bortezomib in myeloma is the Nuclear Factor-Kappa B (NF-κB) canonical pathway. This pathway is inhibited by inhibitor kappa B (IκB) which blocks the nuclear translocation of the heterodimeric transcription factor (p50/p65). IκB is a well characterised target of the proteasome, thus proteasome inhibition leads to accumulating levels of IκB and subsequently to a blockade of NF-κB shuttling to the nucleus and further downstream events.[4] Proteasome inhibition leads to an inhibition of cytokine secretion (IL-6, TNF-α), suppression of

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

Keywords: Bortezomib, proteasome inhibitors, multiple myeloma, haematological malignancies.

Concomitant JAK2 V617F positive essential thrombocytemia and BCR-ABL1 positive chronic myeloid leukaemia masked by imatinib therapy for a gastrointestinal stromal tumour

E. Del Biondo, H. De Raeve, G. Huysmans, K. Hendrickx, E. Wouters, P. Vandenberghe, P. Meeus

The coincidence of a Janus Kinase 2 (JAK2) V617F positive myeloproliferative neoplasm (MPN) and a BCR-ABL1 positive chronic myeloid leukaemia (CML) is rare. We present a patient whose bone marrow and peripheral blood showed typical features of essential thrombocytemia (ET). However, the normalisation of the white blood cell (WBC) count after therapy with imatinib for a gastrointestinal stromal tumour (GIST) suggests that an underlying CML was masked, as witnessed by the very low levels of BCR-ABL1 at the haematological diagnosis. The question remains if this is a case of two separate myeloid malignancies or a secondary event (BCR-ABL1 fusion) in a primary JAK2 V617F + ET.

(Belg J Hematol 2012:3:105-107)

Introduction

The coincidence of a JAK2 V617F positive MPN and a BCR-ABL1 positive CML is rare. So far, a total of six cases with coexistence of ET and CML have been reported in the literature.[1-6] The mechanism of this coexistence has not been established yet.

Case Report

A 72-year old man was admitted to the emergency department with a perforation of the small intestine. Biopsies of the resected segment showed a GIST. *(Figure 1)*. The patient also had a leukocytosis of 13,14 x10^9/l (without immature granulocytes or basophilia) and a platelet count of 968 x10^9/l. Imatinib mesylate 400 mg daily was started as an adjuvant therapy during six months. After this period, the leukocyte count had normalised but the platelet count remained high. Therefore a bone marrow examination was performed. The biopsy was compatible with ET based on an increased number of megakaryocytes with large indented bizarre nuclei. Erythropoiesis and granulopoiesis showed a normal maturation. *(Figure 2)* PCR for JAK2 showed the V617F mutation with an allelic burden of 21%. PCR for BCR-ABL1 was posi-

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Keywords: Essential thrombocytosis, JAK2 V617F mutation, chronic myeloid leukaemia, BCR-ABL1, gastrointestinal stromal tumour

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Current Clinical Trials

(Belg J Hematol 2012;3:108)

Risk Stratified Sequential Treatment for CD20-positive PTLD: an international Phase II trial

PTLD – rituximab – R-CHOP

Posttransplant lymphoproliferative disorder (PTLD) following solid organ transplantation is a rare but life threatening disorder. Although reduction of immune suppression is necessary as first line treatment, this therapeutic option will only lead to a lasting remission in a minority of patients. Most used second therapeutic interventions include the use of rituximab and chemotherapy, both in monotherapy or combined.

In 2002 the European PTLD-1 group initiated this phase II non-randomised open label trial investigating the efficacy, safety and tolerability of sequential therapy with four weekly courses of single agent rituximab, followed by four courses of R-CHOP21 immunochemotherapy in patients with CD20 positive PTLD. Based on an interim analysis, a protocol amendment testing risk stratification based on initial response to rituximab was made in 2007. Patients in complete remission after four courses of rituximab are considered low risk and will receive four additional courses of rituximab every three weeks. Patients not achieving a complete remission are considered high risk and will proceed with four cycles of R-CHOP with G-CSF support (risk stratified sequential treatment). This trial is currently recruiting patients in Australia and several European countries, including Belgium (University Hospital Ghent, Heilig-Hartziekenhuis Roeselare, Cliniques Universitaires UCL Saint-Luc, University Hospitals Leuven).

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The EBMT Congress in Geneva

T. Lodewyck

From April 1 till 4 2012, the 38th Annual Meeting of the European Group for Blood and Marrow Transplantation (EBMT) was held in Geneva. The field of stem cell transplantation keeps on growing, with more than 30,000 transplants being reported to the EBMT in 2010. Some of the highlights of this meeting are briefly summarised.
(Belg J Hematol 2012;3:109-111)

TCR-gene editing

Adoptive immunotherapy remains a field of active investigation. Transfer in T-lymphocytes of T-cell receptor (TCR) genes directed against tumour-specific antigens is a promising technique but has two limitations. First, these T-lymphocytes still express their endogenous TCR leading to competition with the transferred TCR and reduced TCR expression. Second, mispairing of TCR chains may happen and result in reactivity against autologous antigens. Provasi and colleagues received the 'Van Bekkum Award' for the development of a technique based on a Zinc Finger-mediated disruption of endogenous TCR genes combined with transfer of genes encoding for a tumour-specific TCR. Wilm's tumour antigen 1 was selected as antigen in their experiments. This resulted in the production of TCR-edited instead of conventional TCR-transferred lymphocytes, uniquely expressing the tumour-specific TCR at high levels. In a mouse model of leukaemia, infusion of TCR-edited cells resulted in superior event-free survival (EFS) when compared to TCR-transferred or unmanipulated cells.

Matched related and unrelated donors

The Berlin-Frankfurt-Münster (BFM) study group evaluated 387 paediatric patients with high-risk ALL who received stem cell grafts from matched sibling donors (MSD, n=97), matched unrelated donors (MUD, n=251) or mismatched unrelated donors (MMUD, n=39). T-cell depletion was performed in case of unrelated donors. No difference in the incidence of relapse (18% vs 20%), non-relapse mortality (NRM, 5% vs 8%) and EFS (70% vs 68%) was observed between MSD and MUD allogeneic stem cell transplantation (alloSCT). The cumulative incidence of chronic extensive graft-versus-host disease (GVHD) after MUD alloSCT was low and comparable to MSD alloSCT (15% vs 12%), due to use of antithymocyte globulin. By contrast, alloSCT with MMUD resulted in inferior outcome due to an increased NRM of 22%.

AlloSCT for FLT3-mutated AML

The burden of Fms-like Tyrosine Kinase Internal Tandem Duplication (FLT3ITD) mutations (ratio of FLT3ITD to wild type-FLT3 allele) is of major prognostic importance for AML patients harbouring these mutations. In order to estimate the effect of alloSCT in FLT3ITD mutated AML, the survival of patients with mutant rates <0.8 and ≥ 0.8 was analysed. Disease-free survival and Overall survival (OS) at three years from transplantation were comparable between the low-mutation (<0.8) and high-mutation (≥ 0.8) cohort (58% vs 50% and 61% vs 59%, respectively) and significantly superior to FLT3ITD mutated patients lacking a matched donor. These data show that alloSCT might overrule the negative prognostic impact of a high allelic burden in FLT3ITD mutated AML.

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Best of EHA

A. Bosly

The six best abstracts submitted at the European Hematology Association (EHA), 17th Meeting, 2012, Amsterdam were selected for the presidential symposium. Two of them were related to the whole exome analysis: one in T-acute lymphoblastic leukaemia (T-ALL) and one in multiple myeloma (MM).

(Belg J Hematol 2012;3:112-113)

T-ALL

T-ALL is caused by accumulation of somatic mutations. In order to gain insight in the spectrum of mutations present in adult and pediatric T-ALL, K. De Keersmacker et al from Leuven (Belgium) performed a whole exome sequencing on 36 paired diagnosis/remission T-ALL patients plus eighteen diagnosis only and on seventeen T-ALL cell lines. Thirty-five out of 389 mutated genes were selected because they are recurrently mutated. Eight out of 35 expressed the X chromosome explaining the male predominance in T-ALL. Ten genes are known as oncogene or tumour suppressor genes in T-ALL. Twenty-five are potentially novel oncogenic in T-ALL with function in signal transduction transcriptional or epigenetic regulation.

In seven T-ALL cases (13%) exhibited mutations in genes implicated in ribosomes. Mutation of RPL10 gene was identified in 8,4% of pediatric T-ALL and causes ribosome defect. (# O0567).

MM

N. Bolli et al. from Cambridge (U.K), by the analysis of whole exome explore clonal architecture and genomic evolution in multiple myeloma (MM) by analysis CD138 purified BM cells in 67 patients. They confirmed mutations in previously identified genes KRAS in 25% of cases, BRAF 13%, NRAS 13%, FAM46C 9%, TP53 9%, CCND1 1%.

In same patients BRAF mutation co-occurred with KRAS. Several genes unreported in MM were reported. In 97% of patients, at least two subclones were identified in the diagnosis suggesting that MM is a heterogeneous disease. During evolution some mutations were reported NRAS, TP53 loss.

Lessons from these analyses are:

- A comprehensive list of variants (some unreported).
- MM is heterogeneous at diagnosis and
- genetic changes occurred during evolution.

Clinical importance of this work in the future will be to identify at diagnosis clones likely to be resistant to a given treatment and to assess treatment efficacy post-induction. (# 00571)

T cell dysfunction

G. Ramsay from Barts Cancer Institute (London) explored T cell dysfunction in chronic lymphocytic leukaemia (CLL). T cell from CLL have a profound deregulation of functions. Tumour molecules expressed on B-CLL cells could mediate T cell dysfunction.

High expression of some of these molecules (B7 related) CD200, CD274 and CD276 and CD270 were linked to poor prognosis, and antibodies against these molecules restore T cell synapse in vitro. Lenalidomide blocks tumour cell induced T cell synapse dysfunction by inducing down regulation of these molecules.

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The 6th International Conference on Thrombosis and Haemostasis Issues in Cancer (ICTHIC)

Highlights from the 6th International Conference on Thrombosis and Haemostasis Issues in Cancer (ICTHIC), 20-22 April 2012, Bergamo, Italy.

J.F. Baurain, W. Lybaert

It has become a tradition to hold the biennial International Conference on Thrombosis and Haemostasis Issues in Cancer (ICTHIC) in Bergamo. Bergamo is a quiet town in Northern Italy located on a hilltop beyond the Alps. Over 700 physicians with different backgrounds but the same interest attended the meeting this year from April 20th to April 22nd. The meeting provides a unique opportunity for reviewing the different molecular and clinical findings on thrombosis and hemostasis issues in cancer and for updating the guidelines on prophylaxis and treatment of Venous Thrombo-Embolic Events (VTE) in cancer patients. This congress report covers several key topics: duration of prophylaxis in cancer patients undergoing surgery, prevention in medical cancer patients, type and duration of VTE treatment in cancer patients, place of the newer anti-thrombotic agents in cancer patients and survival advantage of Low-Weight Molecular Heparins (LWMH).
(Belg J Med Oncol 2012;6:114-117)

Prophylaxis in cancer patients undergoing surgery

The first curative treatment for patients with early stage disease is surgery. Therefore, it is important to prevent life-threatening complications such as deep venous thrombosis (DVT) and pulmonary embolism (PE). We have known for a long time that cancer patients are more prone to develop Venous Thrombo-Embolic Events (VTE) when undergoing surgery.[1] Some risk factors have been identified: age >60 years, previous VTE, anaesthesia over two hours, hospitalisation over four days and late-stage disease. It has been shown that UnFractionated Heparins (UFH) can reduce up to 80% of the number of fatal PE in surgical cancer patients. Several studies have reported that Low-Weight Molecular Heparins (LMWH) are better at preventing the onset of VTE. Interestingly, new drugs such as fondaparinux have not shown superiority in prevention of VTE and have even shown a higher risk of bleeding postoperatively. Therefore, prophylaxis with LMWH is now the standard of care in surgical cancer patients. The duration of prophylaxis remains an open question. The observation was made that up to 40% of VTE could appear 21 days postoperatively.[1] Several studies have addressed the question of duration of LMWH-

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