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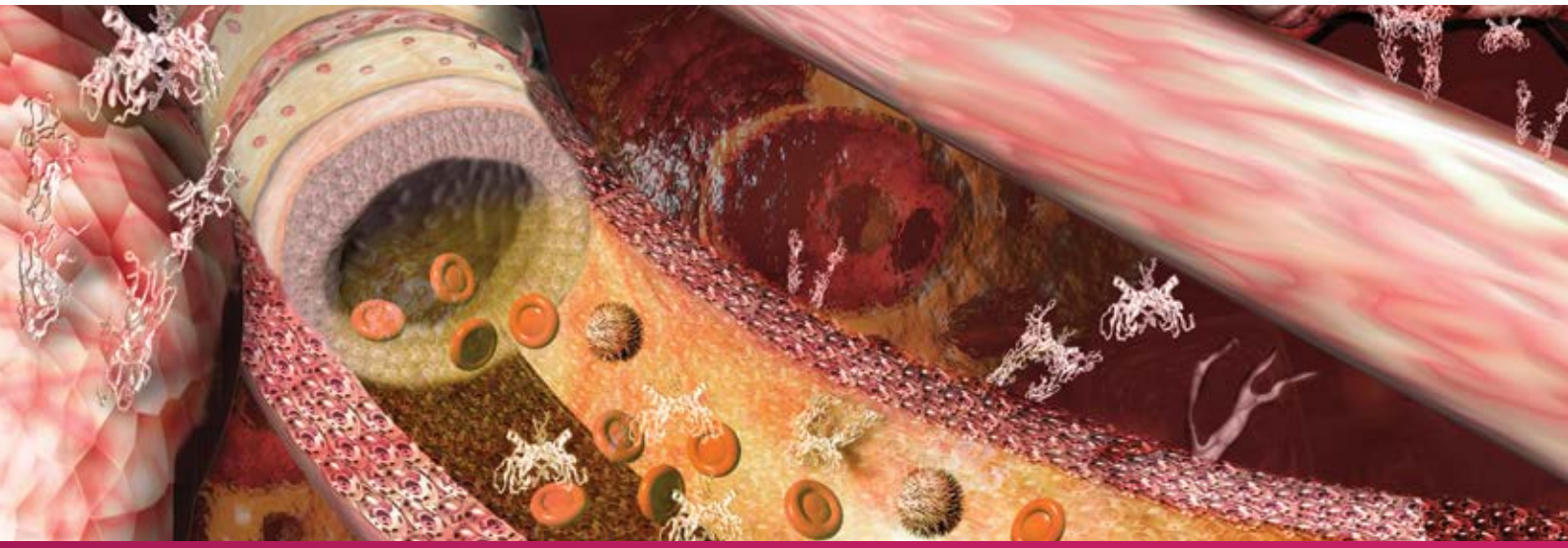

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Belgian Journal of Hematology

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Volume 4, Issue 2, June 2013

Introduction

Dear Reader,

When our patients weren't too bothered by their personal medical problems the last few weeks, two topics kept on recurring during our talks:
The first is of course the long lasting winter and absence of a real spring; though the climatological circumstances mean that you have no excuse not to enjoy some extra reading.

The second is the case of reimbursement or not of a very expensive drug in aHUS. To be able to participate in this discussion, we must be informed in a scientific, correct and unbiased way. I'm convinced the BJH can help in this educational process too.

This edition is again well balanced with clinical guidelines on the use of D-dimers and how to treat large B-cell Non Hodgkin's lymphoma, in first line and in the relapsed setting.

The Antwerp group describes their expertise with immunotherapy in AML. The number of 5.2% (the attentive reader will immediately know what it means) mentioned in their introduction should strike everyone.

We continue with some lighter reading with a trial about pomalidomide in refractory myeloma, a hematocase about Kikuchi-Fujimoto disease and a thesis about haemophilia.

We're happy to have the summary of the BVAC/ABCA program of last January in this issue and conclude with the calendar of events.

I wish you enjoyable reading,

Dr Jan Van Droogenbroeck
Editor in chief

The place of the determination of D-dimer and its improvement

L. Rozen, D. Noubouossie, A. Demulder

D–dimer (DD) assay is a widely used laboratory test in thrombosis-related conditions because it is rapid and easy to perform. This test is highly sensitive to thrombus formation and degradation. However DD levels are increased in many clinical conditions so that its positive predictive value is poor. Improvements of its usefulness have been mainly realised by combining the test with clinical scores and by adapting positive threshold to particular settings of patients. In this article, different methods of DD testing are presented with the aim to review their benefits and pitfalls in various clinical applications.

(Belg J Hematol 2013;4(2):47-50)

Introduction

D-dimer (DD) is a specific product of fibrin degradation. It is formed at the end of the coagulation cascade when cross-linked fibrin is broken by plasmin. A variety of different qualitative and quantitative assays are available for DD testing and are all based on the use of monoclonal antibodies. DD assays are performed by using different techniques: latex particle agglutination either performed manually (semi-quantitative method) or in automated assays using turbidimetry on a coagulometer, and enzyme linked inmmunosorbent assay (ELISA). ELISA and automated latex immunoassays are quantitative assays with a similar sensitivity.[1] DD assays are not standardised so that references ranges and clinical cut-off are not comparable from one assay to the other. Performances of different tests are also widely variable.[1] Most common clinical applications of DD determination are: the diagnosis of venous thromboembolism (VTE) and pulmorary embolism (PE) and the identification of patients at risk of VTE or PE recurrence. It is also a potential tool to determine the optimal duration of anticoagulation treatment and the diagnosis and monitoring of disseminated intravascular coagulation (DIC).

Physiology of D-dimer generation

Figure 1 summarises the step wise process of formation of fibrin and its degradation to generate DD fragments and other products of fibrin degradation.

VTE and PE diagnosis

Bounameaux et al. were the first to suggest a potential usefulness of DD assay to exclude PE.[3] Nowadays it is not recommended to use DD as a standalone test but to request it in combination with a pretest clinical probability (PCP) to exclude VTE or PE.[4] This obviates the need for imaging in a significant number of patients. The most used PCP is the "Well's scoring system".[5] In a recent review over D-Dimer testing, this score was adapted by Tripodi, so that it can stratify patients as having a low, moderate or high probability of DVT or PE.[6] Quantification of DD by Elisa or automated turbidimetric assays has been shown to be highly sensitive in acute DVT or PE (sensitivity>98%).[3] The cut-off value or DD

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

Key words: VTE, PE, D-dimer, DIC, thrombosis recurrence.

Guidelines for newly diagnosed diffuse large B-cell lymphoma (DLBCL) and relapsed DLBCL

G. Verhoef, W. Schroyens, D. Bron, C. Bonnet, V. De Wilde, A. Van Hoof, A. Janssens, D. Dierickx, M. André, E. Van Den Neste

The guidelines for adult patients in this article are based on 2011 ESMO and NCCN version 4.2011 guidelines and amended for the particular Belgian context of label prescription and reimbursement. Levels of evidence for the use of treatment recommendations are given in square brackets. Statements without grading were considered justified standard clinical practice by the experts of the BHS-lymphoma working party.

(Belg J Hematol 2013;4(2):51-57)

Incidence

DLBCL is the most common type of lymphoma with an incidence of three to five cases per 100.000 inhabitants and is increasing with age.[1] This brings the incidence in Belgium to 600 new cases per year.

Diagnosis

Pathological diagnosis should be made on surgical lymph node biopsy or extranodal tissue providing sufficient material for histologic samples including immunohistochemistry. In patients >50 year an EBV stain is recommended. Core needle biopsy is discouraged. It is recommended to collect fresh frozen material for molecular characterisation. Gene expression profiling is at the time investigational. Incorporation of this information into treatment guidelines awaits further investigation. The pathological report should give the diagnosis according to the WHO 2008 criteria.

Staging and risk factors

The staging workup should include patient history and complete physical examination, performance status and systemic complaints (B-symptoms), complete blood count, blood chemistry including LDH, screening for hepatitis B and C, HIV, protein electrophoresis, bone marrow aspirate and biopsy. Computed tomography of the chest, abdomen and pelvis is mandatory. Combination of CT/18F deoxyglucose positron emission tomography is

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Key words: diffuse large B-cell lymphoma, guidelines.

Therapeutic vaccination against acute myeloid leukaemia using dendritic cells

S. Anguille, Z. Berneman

The prognosis of patients with acute myeloid leukaemia (AML) remains dismal, with a five year overall survival rate of only 5.2% for the continuously growing subgroup of AML patients older than 65 years. These patients are generally not considered eligible for intensive chemotherapy and/or allogeneic haematopoietic stem cell transplantation, emphasising the need for novel, less toxic treatment alternatives for the older-age category of AML patients. It is within this context that immunotherapy has gained attention in recent years. In this review, we focus on the use of dendritic cell (DC) vaccines for immunotherapy of AML. DCs are the central orchestrators of the immune system bridging innate and adaptive immunity and are critical to the induction of anti-leukaemia immunity. Here, we discuss the rationale and basic principles of DC-based therapy for AML and review the clinical experience that has been obtained so far with this form of immunotherapy in patients with AML.
(Belg J Hematol 2013;4(2):58-65)

Introduction

The prognosis of adult patients with acute myeloid leukaemia (AML) remains dismal, despite major therapeutic advances over the past decades.[1] This holds particularly true for the continuously growing subgroup of elderly AML patients (>65 years), the latest reported five year overall survival rate being only 5.2%. These patients are generally not considered eligible for intensive chemotherapy and/or allogeneic haematopoietic stem cell transplantation, emphasising the need for more effective and less aggressive treatment alternatives in this particular category of patients.[1]

It is within this context that immunotherapy has come to the fore in recent years.[2] It has been known for a long time that tumour cells, including leukaemic cells, can be recognised and destroyed by the immune system. This paradigm, along with a better understanding of the intricacies of the immune system and its role in tumour control, has stimulated the development of immune-based strategies to treat cancer. One of these strategies involves the use of dendritic cells (DCs), the key orchestrators of the immune system. DCs are key to the induction of anti-leukaemia immunity, explaining the importance and potential of these cells for immunotherapy of AML.[1]

In this article, after introducing the basic principles of DC-based therapy for AML, we will review the clinical experience that has been obtained so far with this form of immunotherapy in patients with AML. We conclude by discussing possible directions for

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

Key words: dendritic cells, vaccination, immunotherapy, acute myeloid leukaemia.

A rare cause of lymphadenopathy in a young woman: the Kikuchi-Fujimoto disease

E. Philipse, T. Martens, A. Bufi, M. Kockx, P. Zachee, K. Wu

A 16-year-old Moroccan woman was referred to our centre because of bilateral cervical lymphadenopathy, high fever and weight loss. A malignant lymphoma was suspected in the lymph node biopsy. Histopathologic review of the lymph node biopsy showed extensive necrosis and nuclear debris with no viable remaining cells. A new lymph node biopsy was performed and the diagnosis of histiocytic necrotising lymphadenitis (Kikuchi-Fujimoto disease) was made. This is a rare, benign and self-limiting disease that mainly affects young woman.

Belg J Hematol 2013;4(2):66-69)

Introduction

Cervical lymphadenopathy is common in children of all ages and adolescents. Most cases of cervical lymphadenopathy are self-limiting and resolve spontaneously in a few weeks. It is usually caused by a viral or bacterial infection located in the nose, throat or ear. Uncommon and rare causes of cervical lymphadenopathy are cat scratch disease (Bartonella), toxoplasmosis, tuberculosis, collagen vascular disease and neoplastic diseases such as lymphoma. In this article we describe a case of a 16-year-old woman with cervical lymphadenopathy, fever and weight loss due to Kikuchi-Fujimoto disease, a benign and self-limiting disease.

Case report

A 16-year-old Moroccan woman was referred to our centre with painful enlarged cervical lymph nodes since one month. This was accompanied by high fever, anorexia, weight loss and generalised muscle pain. The medical history was unremarkable and antibiotics did not result in any improvement. A lymph node biopsy was performed and a malignant lymphoma was suspected.

Physical examination revealed a blood pressure of 100/70 mmHg and a temperature of 40° Celsius. Large confluent bilateral cervical lymph nodes of four centimeters were noted. There was no axillary or inguinal lymphadenopathy. General internal-medical examination revealed no abnormalities, in particular no hepatosplenomegaly.

Laboratory tests showed an erythrocyte sedimentation rate of 88 mm/h, a hemoglobin count of 8.5 g/dl, a leukocyte count of 1,1 x 10^9/l with 63.2% neutrophils, 3.6% eosinophils, 0.0% basophils, 29,0% lymphocytes and 4.1% monocytes. The liver tests were abnormal: aspartate aminotransferase (AST) 236 U/l, alanine aminotransferase (ALT) 115 U/l and lactate dehydrogenase (LDH) 5645 U/l *(Table 1)*. Serologic tests for human immunodeficiency virus (HIV), cytomegalovirus (CMV), Epstein-Barr virus (EBV) and parvovirus B19 were negative. Mycoplasma

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

Key words: Lymphadenopathy, histiocytic necrotizing lymphadenitis, Kikuchi-Fujimoto disease, systemic lupus erythematosus.

Current Clinical Trials

(Belg J Hematol 2013;4(2):70-71)

A multicentre, single-arm, open-label study with pomalidomide in combination with low dose dexamethasone in subjects with refractory or relapsed and refractory multiple myeloma (CC-4047-MM-010)

Multiple Myeloma, pomalidomide, double refractory

Background

Multiple myeloma (MM) is an incurable disease that will progress to resistant disease. MM patients who have become refractory to novel agents bortezomib (BORT) and lenalidomide (LEN) have a poor prognosis, with a median overall survival (OS) of nine months.[1] Pomalidomide (POM) is a new immunumodulator drug with the same toxicity profile than lenalidomide. A phase 3 study in double refractory (LEN+BORT) MM has shown that comparing to high-dose dexamethasone, POM plus low-dose dexamethasone (LD-DEX) significantly increases the progression free survival (PFS) (median 15.7 vs 8.0 weeks; P<.001) and the OS (median not reached vs 34 weeks; P<.001).[2]

Trial

This trial is a multicentre, single-arm study that evaluates the safety of POM and LD-DEX combination in a large cohort of subjects with refractory or relapsed and refractory MM. Eligible patients must have a measurable disease. They must have either of the two: 1) a BORT and LEN resistant disease defined as a progressive disease during the treatment or within 60 days of the end of the treatment, 2) a BORT and LEN relapsed and refractory disease defined as a relapsed disease within the six months after the end of the treatment and must be refractory to their last treatment. Before referring patients some important exclusion criteria must be checked: the renal function (creatinine clearance must be ≥45ml/min); the blood count (platelet ≥75,000/μL or ≥30,000/μL if there is a bone marrow cell infiltration ≥50%; absolute neutrophil >1,000/μL) and the absence of a peripheral neuropathy ≥Grade 2.

Conclusions and recommendations

- Double refractory MM have a poor prognosis and short survival.
- In this population, POM LD-DEX is the sole treatment that has demonstrated a significantly increase of EFS and OS in a phase 3 trial.
- This single arm trial is an opportunity for those bad prognosis patients.

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Functional assessment of haemophilic arthropathy with three-dimensional gait analysis

S. Lobet, C. Hermans

In patients with haemophilia, the long-term consequences of repeated haemarthrosis include joint cartilage damage and irreversible chronic arthropathy, resulting in severe impairments in locomotion. Quantifying the extent of joint damage is of paramount importance in order to prevent disease progression and compare the efficacy of treatment strategies, such as prophylaxis. Here we summarise the results of several studies establishing three-dimensional gait analysis as an innovative approach to evaluate functionally haemophilic arthropathy. This work also provides new insights into the understanding of the biomechanical consequences of haemophilic arthropathy.
(Belg J Hematol 2013;4(2):72-76)

Introduction: Assessment of musculoskeletal complications of haemophilia

In patients with haemophilia (PWH), approximately 80-90% of bleeding episodes occur in the musculoskeletal (MSK) system, especially in the large synovial joints, as well as in the muscles. These recurrent haemarthroses induce progressive cartilage damage, leading to joint destruction and subsequent severe functional limitation.

With respect to haemophilia, the MSK assessment has traditionally been performed using both radiological and clinical joint scoring systems. However, clinical joint scoring may not be sensitive to detect subtle changes in joint status and radiological examination does not provide an understanding of the causes underlying these impairments.
In this paper, we explore a new approach to the functional assessment of MSK complications in PWH by means of a specialised laboratory equipment to study biomarkers of human motor performance with three-dimensional gait analysis (3DGA).

3DGA as a new tool to explore the MSK impairments in haemophilia

In 3DGA, biomechanics analysis variables are used to pinpoint which joint or muscle system is responsible for the functional defect. Contrary to radiological and clinical examinations performed in a supine position, the uniqueness of 3DGA is that it assesses the patient during the act of walking, i.e., under weight-bearing conditions. This is of the utmost importance, as pain induced by weight-bearing activities influences the functional performances of the arthropathic joints significantly.

A digital video-based motion analysis system analyzes the kinematic part of locomotion. Kinematic analysis measures the active range of motion (ROM) of a joint. While the patient is walking on a treadmill,

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Conflict of interest: The authors have nothing to disclose and indicate no potential conflict of interest.
Key words: haemophilia, gait analysis, biomechanics, walk, arthropathy, osteoarthritis, physiotherapy, rehabilitation, function.

Summary of the BVAC/ABCA program hosted by the general annual meeting of the BHS in Ghent, Friday January 25th 2013

A. Kornreich, A. Gothot

For the first time, during the course of its general annual meeting, the BHS hosted a satellite meeting organized by the Belgian Society for Analytical Cytology (BVAC/ABCA) to bring together clinicians with laboratory scientists and staff. The BVAC/ABCA program included state-of-the-art lectures, followed by a session focused on advances in genetic testing of haematological malignancies and finally a satellite symposium sponsored by Alexion on the deficiencies of complement regulators leading to thrombotic micro-angiopathies (TMA). All these presentations are available on the BVAC/ABCA website: http://www.cytometry.be/Gent2013.html

(Belg J Hematol 2013;4(2):77-82)

State-of-the-art lectures

1. Immune monitoring in intensive care patients

(Guillaume Monneret, PharmD, PhD,Cellular Immunology Unit, E. Herriot Hospital, Lyon, France)

Sepsis is still a leading cause of death in intensive care units and its incidence is higher than most common diseases. Recent data suggest that after the initial proinflammatory phase of immune activation, a protracted phase of immune suppression is ultimately responsible for viral reactivation, nosocomial infections and mortality. The objective of monitoring ICU immunodepression is to identify patients who could most benefit from immune stimulation. The best tools to achieve immune monitoring are based on flow cytometry.

Septic patients have a marked reduction in absolute T-, B- and NK-cell counts at diagnosis. Lymphocyte apoptosis leading to defective restoration of T-cell counts after one week is predictive of mortality. In addition, an increased proportion of circulating regulatory T-cells (Treg; CD4+CD25+CD127-) is observed in sepsis, and contributes to lymphocyte anergy.

Currently, the best characterized marker of immune suppression is the decreased expression of HLA-DR on monocytes (mHLA-DR), which is a surrogate marker of their function. In septic shock, low mHLA-DR expression is independently associated with nocosomial infections and its persistent low expression predicts mortality. Additionally, it predicts unfavourable outcome and nosocomial infections in other ICU conditions (major trauma, acute pancreatitis, severe burn injury, acute stroke, decompensated liver cirrhosis), in paediatric lung transplant recipients and is correlated with the

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October 4-6	**ESH International Conference on Multiple Myeloma** Dublin, Ireland For more information please visit: http://www.esh.org/conferences/
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