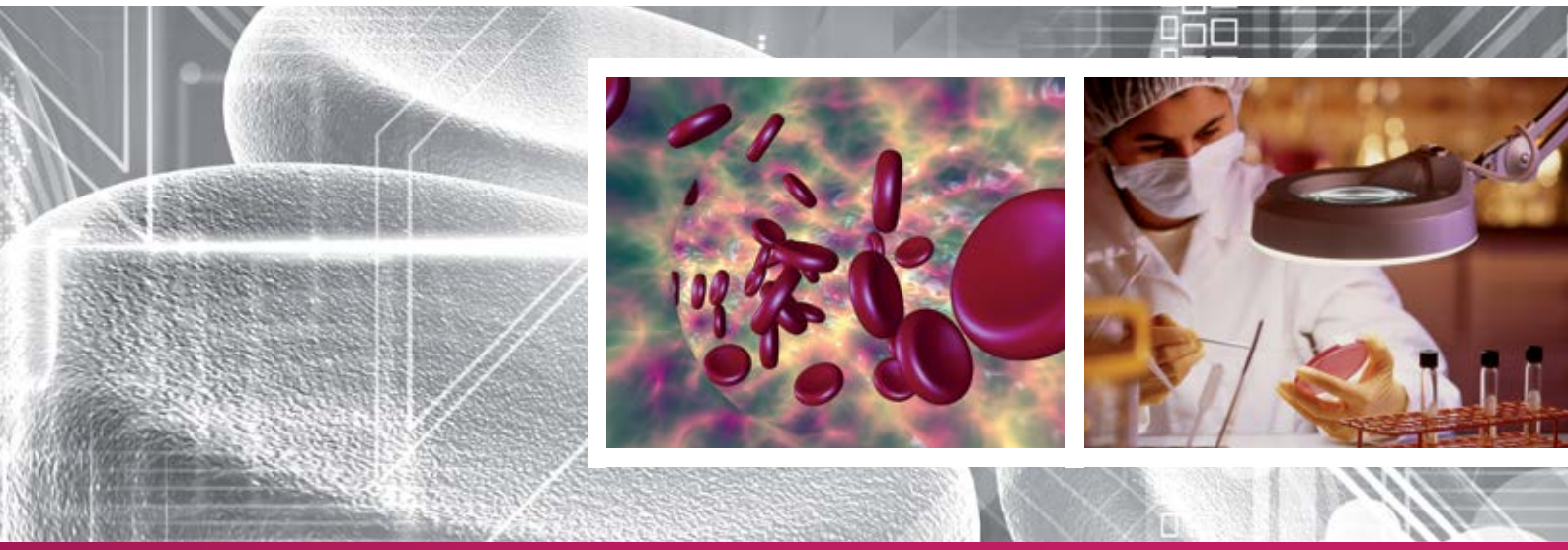
Belgian Journal of Hematology

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)

Volume 3, Issue 4, December 2012



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colophon

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Volume 3, Issue 4, December 2012

Introduction

Dear Reader,

As 2012 is quickly approaching its end, I do hope every one of you can reflect on a successful and interesting year. On behalf of the BJH editorial board, please accept our best wishes for you and your loved ones for 2013!

I hope that you find the time somewhere in your busy schedules consisting of clinics, ASH, holiday period, and post-ASH, to read this issue of the BJH.

Our first article gives a review of the treatment of post transplant lymphoproliferative disorders following solid organ transplantation. The second article covers T-cell/histiocyte-rich large B-cell lymphoma; both are rare malignancies, but deserve a clear review with relevant information for the clinician when confronted with one of these.

We are especially proud of the BHS guidelines for the treatment of chronic lymphoid leukaemia anno 2012 printed in this issue. These guidelines are the fruit of a joined effort between nine experts in the field, and are discussed by Prof. A. Bosly, whose passion for B-cell lymphoproliferative disorders is well known.

This issue is bolstered with an article on brentuximab vedotin (pharmacotherapy), a series of a very rare form of lymphoma (case report), and the BLAST trial (clinical trial).

The final contribution looks at the possible application of microvesicles in several haematological disorders.

I wish you enjoyable reading,

Jan Van Droogenbroeck, MD, PhD
Editor in chief

Treatment of posttransplant lympho-proliferative disorders following solid organ transplantation

D. Dierickx, X. Vanoeteren, G. Verhoef

Prevention of organ rejection following solid organ transplantation requires long term immunosuppressive therapy, leading to an increased risk of both infections and malignancies. Although skin cancers are the most common malignancies, posttransplant lymphoproliferative disorder (PTLD) comprises one of the most serious complications following transplantation with high morbidity and mortality rates. Here we will review current treatment options for PTLD following solid organ transplantation (SOT).

(Belg J Hematol 2012;3: 121-127)

Introduction

Posttransplant lymphoproliferative disorder (PTLD) is a rare but life threatening disorder following both solid organ and hematopoietic stem cell transplantation.[1,2] The disorder is characterised by an uncontrolled proliferation of lymphocytes, caused by medication induced diminished immune surveillance. From a pathological point of view PTLD has a broad and heterogeneous spectrum of appearance, ranging from a benign condition to an aggressive lymphoma. Although not required for diagnosis of PTLD, Epstein Barr virus (EBV) plays a major role in the pathogenesis of the majority of PTLDs.[3] Currently the gold standard in diagnosis of PTLD remains biopsy with histopathologic examination to categorise every case according to the World Health Organization 2008 classification. In this way the WHO classification distinguishes four major PTLD subtypes: (1) early lesions, (2) polymorphic PTLD, (3) monomorphic PTLD (fulfilling the criteria of B-, T-, NK- or plasma cell neoplasms) and (4) classical Hodgkin-type PTLD.[4] Similar to its heterogeneous presentation treatment options are diverse and may include preventive, preemptive, curative and palliative approaches. However, the backbone of all PTLD therapies –except maybe for real palliation– should be (partial) reconstitution of the immune system. As development of PTLD is the consequence of an imbalance between immunosuppression and immunosurveillance, different approaches can be made in the treatment of the disorder. These approaches include improving reconstitution of the immune system, targeting the uncontrolled proliferation of malignant B cells and decreasing (EBV) viral load.[5] Unfortunately treatment for PTLD is largely based on retrospective data with only few prospective and no randomised trials being performed until now. As a consequence formal recommendations are lacking and currently treatment is largely physician or transplant centre dependent.

Taking into account that PTLD is always associated with a high degree of overimmunosuppression, the most important therapeutic intervention seems to be reduction of immunosuppression, leading to (partial) cellular (EBV specific) immunity reconstitution. However, in many cases this is insufficient and

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

Key words: posttransplant lymphoproliferative disorder, PTLD, solid organ transplantation, transplantation, treatment.

T-cell/histiocyte-rich large B-cell lymphoma: review on pathologic diagnosis, current therapeutic options and new targets for therapy

J. Cornillie, T. Tousseyn, G. Verhoef

T-cell/histiocyte rich large B-cell lymphoma (THRLBCL) is a rare variant of diffuse large B-cell lymphoma (DLBCL) with an aggressive behaviour. Clinically, THRLBCL affects a young, predominantly male population. Pathologically, it is characterised by fewer than 10% of large neoplastic B-cells in a background of abundant T-cells with or without the presence of histiocytes. Differentiating THRLBCL from other lymphoproliferative disorders can be difficult but is achieved by morphologic and immunohistochemical characterisation of the tumour cells in the appropriate stromal microenvironment. Despite these clinical and pathologic differences, treating THRLBCL is not different from treating stage-matched DLBCL and can result in a comparable outcome. Comparative studies, however, on outcome of THRLBCL and DLBCL are methodologically weak and include small numbers of patients. Recently, gene expression profiling showed a predominant role for a distinct host immune response in THRLBCL, leading to tumor tolerance. Targeting specific molecules responsible for this tumour tolerance could lead to novel therapeutic options.

(Belg J Hematol 2012;3: 128-133)

Introduction

Currently, T-cell/histiocyte rich large B-cell lymphoma (THRLBCL) is considered as a rare morphologic variant of diffuse large B-cell lymphoma (DLBCL), representing 1% to 3% of all B-cell lymphomas.[1] In current practice, standard therapeutic regimens for DLBCL are also applied for THRLBCL. Multiple study groups focused on comparing outcome between DLBCL and THRLBCL. Some studies showed comparable outcome,[2-4] another study suggested worse prognosis for patients with THRLBCL compared to DLBCL.[5] This dichotomy results in uncertainty about the best therapeutic options when THRLBCL is diagnosed. This review discusses the clinical and biological differences between DLBCL and THRLBCL and aims at formulating recommendations for optimal treatment of THRLBCL.

T-cell/histiocyte-rich large B-cell lymphoma

Clinical characteristics

Clinical features of patients included in four previously published clinical series on THRLBCL are shown in *Table 1*. According to these data THRLBCL affects a

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

Key words: T-cell/histiocyte rich large B-cell lymphoma (THRLBCL); diffuse large B-cell lymphoma (DLBCL); Rituximab-CHOP; tumour microenvironment

BHS guidelines for the treatment of chronic lymphocytic leukaemia anno 2012

A. Janssens, E. Van Den Neste, W. Schroyens, M. André, A. Van Hoof, V. De Wilde, G. Verhoef, F. Offner, D. Bron, on behalf of the BHS Lymphoproliferative Working Party

Tremendous improvements in treatment outcome have been obtained over the past decade but for most of the patients chronic lymphocytic leukaemia (CLL) still remains an incurable disease. We eagerly await tools incorporating patient related, disease related and treatment related factors, in order to balance efficacy and toxicity and to personalise treatment in a more rational manner. No treatment is necessary for patients without active and/or advanced disease, regardless of prognostic factors. When treatment is indicated we recommend fludarabine, cyclophosphamide, rituximab (FCR) as front-line strategy for fit patients, bendamustine, rituximab (BR) for patients unfit for FCR and chlorambucil for older patients with a geriatric profile or patients with major comorbidities or a reduced performance status. The choice of treatment for patients with recurrent advanced and/or active disease depends on the duration of response to the previous treatment and on the type of treatment refractoriness. Reduced intensity conditioning allogeneic stem cell transplantation should be considered for patients with a de novo or an acquired 17p deletion, for patients refractory to F, or F and alemtuzumab, or for patients with an early relapse after chemo-immunotherapy.

We encourage patients to enter clinical trials exploring new agents. Among these new approaches, the signal transduction inhibitors have shown remarkable activity in very advanced disease, independent of genetic aberrations.

(Belg J Hematol 2012;3: 134-143)

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W. Schroyens, A. Van Hoof, V. De Wilde, F. Offner have nothing to disclose and indicate no potential conflict of interest.

Key words: chronic lymphocytic leukaemia, treatment guidelines

Chronic lymphocytic leukaemia: accessibility for Belgian patients to recommended treatments?

Editorial for the contribution of A. Janssens et al, entitled "BHS guidelines for the treatment of chronic lymphocytic leukaemia anno 2012"

A. Bosly

(Belg J Hematol 2012;3: 144)

In this issue, Ann Janssens et al published BHS guidelines for the treatment of Chronic Lymphocytic Leukaemia (CLL) anno 2012.[1] This outstanding paper reviewed in detail CLL from diagnosis to treatment. CLL is the most frequent leukaemia in adults and two thirds of patients must be treated either immediately after diagnosis or later during disease course. Recent insights on the pathogenesis are providing more potent treatments in order to modify the objective of treatment: improve survival instead of palliative regimen. Moreover new agents such as Lenolidamide, BTK inhibitors, signal transduction inhibitors, new monoclonal antibodies, apoptosis inducing agents will also probably improve prognosis in the future, and participation of Belgian patients in these clinical trials are highly recommended.

Now the standard treatment is Rituximab-Fludarabine-Cyclophosphamide (FCR, grade of recommendation A) which is only applicable in fit patients and probably only half of the patients can safely receive this treatment. For patients unfit to receive FCR, the recommendation is to replace Fludarabine- Cyclophosphamide by Bendamustine: an original molecule with both alkalating and purine analog characteristics. Bendamustine is less toxic than Fluradabine-Cyclophosphamide and BHS recommendation (B) is to give Rituximab-Bendamustine to unfit patients, according to results of recent publication.[2] Moreover results of BR are encouraging and close to RFC. Now BR is tested versus RFC in prospective randomised trial in the German Group. Chlorambucil is only recommended as first line treatment for older patients with major comorbidities. English experience with Rituximab-Chlorambucil suggests that this regimen obtained better results than Chlorambucil alone and may be an option for elderly patients.[3]

However until now, according to the rules of reimbursement by RIZIV/INAMI, Rituximab can only be given with Fludarabine-Cyclophosphamide and not with Bendamustine or Chlorambucil. On the other hand, Bendamustine can only be given alone for first line treatment and not for relapsing patients.

Modifications of these rules are thus of critical importance in order to offer to Belgian patients the treatment recommended by the BHS guidelines.

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Brentuximab vedotin: an innovative treatment for patients with Hodgkin and systemic anaplastic large cell lymphoma

A. Van Hoof

Brentuximab vedotin is an anticancer antibody-drug conjugate: it comprises an anti-CD30 monoclonal antibody conjugated to MMAE (monomethyl auristatin E), a synthetic tubulin polymerisation inhibitor. The drug is given intravenously every three weeks. It has been used in treatment of relapsed Hodgkin lymphoma (HL) and relapsed systemic anaplastic large cell lymphoma (sALCL). Excellent results were obtained in these indications. Trials are underway in combination with chemotherapy for first line treatment.
(Belg J Hematol 2012;4:145-149)

Introduction

Brentuximab vedotin (BV, ADCETRIS™, SGN-35, Seattle Genetics, Inc, Bothell, WA, USA and Takeda/ Millennium Pharmaceuticals, Inc., Cambridge, MA, USA). is an antibody-drug conjugate. The anti-CD30 antibody is a chimeric antibody that is bound to MMAE, monomethyl auristatin E or vedotin. The antibody is bound to the toxin through a peptide linker. BV is stable in the blood and releases vedotin upon internalisation in CD30 positive tumour cells.[1] CD30 is expressed by Hodgkin cells and by tumour cells in anaplastic large cell lymphoma (ALCL). Some cutaneous T cell lymphoma's are also CD30 +. This review describes the use of BV in these lymphomas.

Hodgkin lymphoma is highly curable in early stages. Patients in stage I and II have an overall five year survival rate of more than 90%. Patients in stage III and IV have a five year survival rate of about 60-85%. When patients relapse, a significant number can be cured with salvage chemotherapy and autologous stem cell transplantation. Patients who progress during first line chemotherapy or who relapse early have a poor outcome. Patients who relapse after autologous stem cell transplantation have a very poor prognosis.[2]

ALCL is one of the peripheral T-cell lymphomas (PTCL). According to the International PTCL study, ALK+ ALCL accounts for 6.6% and ALK-ALCL for 5.5% of PTCL cases. In the group of ALCL, about 50-60% are ALK+ (expression of an ALK fusion protein, which is NPM-ALK in approximately 72% to 85% of cases and consists of a fusion protein containing ALK and other gene product(s) in the remaining cases). Distinction of ALK+ ALCL and ALK− ALCL is clinically important because the former usually affects younger patients and shows a more favourable clinical course. Cure rate in ALK+ ALCL is about 70-85%, in ALK- ALCL about 35-45%. When patients relapse, outcome is usually not good.[3]

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Key words: brentuximab vedotin, Hodgkin lymphoma, systemic anaplastic large cell lymphoma, antibody drug conjugate, neuropathy.

Intravascular large B-cell lymphoma: four case reports from a single centre and review of literature

S. Drieghe, B. Cauwelier, T. Lodewyck, D. Selleslag, J. Van Droogenbroeck, A. Van Hoof, J. Van Huysse, J. Billiet

Intravascular lymphoma is a rare haematological malignancy characterised by neoplastic proliferation of lymphoid cells particularly within the lumina of capillaries, heterogeneity in clinical presentation, disseminated disease with aggressive behaviour and often fatal course. In the present case report, we describe four cases of intravascular lymphoma diagnosed in a single centre over a period of ten years.
(Belg J Hematol 2012;3: 149-154)

Introduction

The WHO classification of tumours of haematopoietic and lymphoid tissues defines intravascular large B-cell lymphoma (IVLBCL) as a rare subtype of extranodal diffuse large B-cell lymphoma (DLBCL) characterised by the selective growth of lymphoma cells within the lumina of vessels, particularly capillaries, with the exception of larger arteries and veins.[1] Few cases of intravascular lymphoma exhibiting a T-cell or Natural Killer-cell phenotype have been described.[2] The heterogeneity of clinical presentation and lack of detectable tumour mass or lymphadenopathy often hampers timely and accurate diagnosis. This is partly reflected in the fact that an IVLBCL usually presents as a widely disseminated lymphoma with an aggressive and rapid progressive clinical course. In recent years, the increased awareness of IVLBCL has resulted in more patients being diagnosed during life, whereas in the past diagnosis was made postmortem. We diagnosed four cases of this rare lymphoma entity in our hospital over a period of ten years. In this paper we give a description of these four cases as well as a review of the literature.

Case reports

Case 1

A seventy-year old woman presented with a two week history of high fever, rigors, anorexia and abdominal pain. A laparoscopic cholecystectomy was performed as cholecystitis was suspected. However, after surgery she developed dyspnoea, kidney failure, elevated LDH levels and haemolytic anemia (positive direct and indirect Coombs). Peripheral blood analysis revealed a low haemoglobin (9,7 g/dL), normal white blood cell count (9,9.10^9/L) with a slight lymphopenia, severe thrombocytopenia (27.10^9/L) and elevated transaminases. As her serum LDH level rapidly raised to 11.955 U/L, a haematological disorder was suspected and a bone marrow trephine biopsy and aspirate were performed. Cytomorphologic

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Key words: intravascular large B-cell lymphoma, diffuse large B-cell lymphoma, extranodal lymphoma, intravascular lymphoma

Current Clinical Trials

(Belg J Hematol 2012:3:155-156)

The BLAST trial for MRD+ adult B-precursor acute lymphoblastic leukaemia (B-ALL) patients investigates a bi-specific anti-CD19/anti-CD3 BiTE® antibody (blinatumomab®)

B-cell precursor acute lymphoblastic leukaemia; BCP-ALL; minimal residual disease; MRD; BiTE®

Background:

Blinatumomab is bi-specific single chain BiTE® antibody designed to redirect cytotoxic T-cells for lysis of B-precursor ALL cells by crosslinking CD3 present on all normal T-cells with CD19 expressed on leukemic cells. This results in perforin- and granzyme-mediated death of the target cell.[1]

Blinatumomab® corresponds to a new class of therapeutic antibodies called 'bispecific T cell engagers' (BiTEs) capable of redirecting any cytotoxic T cell to tumour cells. BiTE® antibodies directed against other target antigens than CD19 are currently investigated in solid tumour indications.[2]

BiTE® antibodies represent a completely new immunotherapeutic approach for cancer therapy that exploits characteristics of both humoral and cellular immune responses, resembling to some extent the tumour allo-specific CTL response expected after hematopoietic stem cell transplantation (HSCT) but without its inherent toxicity.

Blinatumomab has shown a remarkable activity in a phase II study with B-precursor ALL patients for the eradication of minimal residual disease (MRD). The results of the initial phase II study MT103-202 are impressive with 80% of MRD negativity achieved after the first treatment course.[3] Blinatumomab is also currently tested in the context of haematologic relapse/refractory disease in Germany (study MT103-206). Here the activity of blinatumomab is also impressive.[4,5]

Persistence or reappearance of MRD of B-ALL is an indicator of resistance to chemotherapy. In this case, HSCT offers a chance of cure but many patients remain MRD+ and experience relapse before transplantation or are not eligible for transplantation because of older age or lack of donor. Even after transplantation, the prognosis of patients with positive MRD before the procedure remains poor. This is especially the case for relapsed B-ALL.

In this situation where conventional treatment approaches fails, blinatumomab offers a very high rate of conversion to MRD negativity, sometimes sustained, and can be used as a bridge to HSCT.

The BLAST trial:

The BLAST trial is a confirmatory European multicenter, single-arm study to assess the efficacy, safety, and tolerability of the BiTE® antibody blinatumomab® in adult BCP-ALL patients who, after intensive treatment (consisting of at least three blocks of intensive chemotherapy), are in hematologic remission but still have a positive MRD (>10-3).

Blinatumomab is administered as a continuous infusion. If a HSCT is planned, blinatumomab serves as a 'bridge to transplant' by lowering the MRD level before transplant. If there is no graft, four courses of the antibody are planned. It is possible to retreat in case of molecular relapse after blinatumomab.

Practically:

In order to assess the MRD response by molecular techniques, DNA obtained at diagnosis or relapse has to be sent prospectively to the central laboratory in Germany (Kiel) to establish a clonospecific PCR test and confirm the level of MRD at the time of inclusion.

To increase the number of B-ALL patients that can potentially benefit from the drug, the sponsor gives the opportunity to all hematologic centres (this proposal also applies to all the centres where the protocol is not open!) to send DNA from the newly diagnosed B-ALL to the central lab in Kiel, already at the time of diagnosis or relapse, for the lab to establish clonospecific PCR (creation of primers specific to the patient

Then at the end of induction (which must have included at least three blocks of intensive chemotherapy) or at the end of re-induction (when the patient is in hematologic remission) a new sample must be sent to Kiel to determine the MRD. If it is >10-3,

Quantification and characterisation of microvesicles: Applications in hereditary spherocytosis, type-II heparin-induced thrombocytopenia and cancer

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

Microvesicles (MVs) are sub-micron-size cellular fragments released by eukaryotic cells following activation or apoptosis. Their diameter ranges between 30 and 1000 nm. Microvesicles are thought to play a major role in cellular cross-talk, inflammation, thrombosis and angiogenesis. As potential disease biomarkers, MV measurement and characterisation in biological fluids could also reveal new diagnostic and/or prognostic information in human disease. In this work:

- **We developed and validated an easy-to-use and useful quality control parameter for MV analysis by flow cytometry (FCM), the most frequently used technique to study MVs.**
- **We developed and validated a reproducible MV quantification method by FCM in whole blood in order to avoid preanalytical concerns of plasma assays (i.e. loss of MVs by centrifugation and lack of standardisation in centrifugation methods).**
- **We showed that this method could contribute to the diagnosis of hereditary spherocytosis (HS), a haemolytic anemia characterised by a release of MVs and unexplained occurrence of venous and arterial thrombosis after splenectomy.**
- **We developed and validated a high sensitive sizing atomic force microscopy (AFM) method.**
- **We characterised tumour cell-derived MVs released by cultured breast cancer cells MDA-MB 231 (Cells) by FCM, Transmission Electron Microscopy, AFM and Thrombin Generation Assay.**
- **Finally, we developed a platelet microparticle generation assay (PMPGA), a test which reproduces the in vivo type II heparin-induced thrombocytopenia (HIT) reaction. We showed that this assay, presented at least similar performances in comparison to the current biological reference, i.e. ^{14}C-Serotonin Release Assay. As flow cytometry is widespread available, PMPGA**

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