Post-transplant lymphoproliferative disorder: a heterogeneous conundrum

In a recent paper in this journal, Montanari et al (2015) reported a detailed analysis of prognostic factors in a large series of patients with post-transplant lymphoproliferative disorder (PTLD) and developed a prognostic score which they suggested could be used for risk stratification and enrolment in clinical trials. However, the many different disease entities included under the rubric of PTLD makes this an exercise in futility.

A recent review (Dierickx et al, 2015) and expert workshop (Glotz et al, 2012) have called for an improved classification of PTLD in order to better understand the changing incidence and varied pathogenesis and biology, as well as the risk factors, prognostic indicators and responses to treatment of this heterogeneous group of disorders. A better classification of PTLD would also facilitate improvement of clinical trial design and enable comparison of treatment strategies for specific disease entities across different well-designed trials, in contrast to the rather confusing state of our current knowledge (Trappe et al, 2012; Dierickx et al, 2013; Kinch et al, 2014; Luskin et al, 2015).

The current 2008 World Health Organization classification of PTLD (Swerdlow et al, 2008) has contributed to the lack of precision in clinical trials. However, the many different disease entities included under the rubric of PTLD makes this an exercise in futility.

Table I. Proposed classification of lymphoproliferative disorders occurring after organ transplantation.

<table>
<thead>
<tr>
<th>Classification</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>1. Benign and reactive disorders, EBV+ and polyclonal</td>
<td>Classified according to subtype</td>
</tr>
<tr>
<td>2. Indolent plasma cell proliferations, EBV+ and clonal</td>
<td>Classified according to subtype</td>
</tr>
<tr>
<td>3. Post-transplant lymphoproliferative disorders (true PTLD), always EBV+ and either polyclonal, oligoclonal or monoclonal</td>
<td>Classified according to subtype</td>
</tr>
<tr>
<td>a. Indolent plasma cell proliferations</td>
<td>EBV+ and either polyclonal, oligoclonal or monoclonal</td>
</tr>
<tr>
<td>b. Florid follicular hyperplasia</td>
<td>EBV+ and either polyclonal, oligoclonal or monoclonal</td>
</tr>
<tr>
<td>c. Infectious mononucleosis</td>
<td>EBV+ and either polyclonal, oligoclonal or monoclonal</td>
</tr>
<tr>
<td>d. Mucocutaneous ulcer</td>
<td>EBV+ and either polyclonal, oligoclonal or monoclonal</td>
</tr>
<tr>
<td>e. Polymorphic and monomorphic PTLD</td>
<td>EBV+ and either polyclonal, oligoclonal or monoclonal</td>
</tr>
<tr>
<td>4. Malignant lymphomas, usually EBV+ (some subtypes may be EBV+) and clonal</td>
<td>Classified according to subtype and EBV status</td>
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<tr>
<td>a. Non-Hodgkin lymphomas, B-cell types, indolent or aggressive</td>
<td>Classified according to subtype and EBV status</td>
</tr>
<tr>
<td>b. Non-Hodgkin lymphomas, T-cell or NK-cell types, usually aggressive</td>
<td>Classified according to subtype and EBV status</td>
</tr>
<tr>
<td>c. Hodgkin lymphoma</td>
<td>Classified according to subtype and EBV status</td>
</tr>
<tr>
<td>d. Plasma cell myeloma</td>
<td>Classified according to subtype and EBV status</td>
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</tbody>
</table>

EBV, Epstein–Barr virus; NK, natural killer; PTLD, post-transplant lymphoproliferative disorder.
of significant progress in our understanding of PTLD by grouping the various disease entities together into heterogeneous categories (early lesions, polymorphic PTLD, monomorphic PTLD and classical Hodgkin lymphoma type PTLD) without regard for Epstein–Barr virus (EBV) infection status or clonality of the various entities in these categories. For example, the category of monomorphic PTLD includes polyclonal, oligoclonal and monoclonal EBV-driven B-cell proliferations due to severe immunosuppression, as well as true non-Hodgkin lymphomas of many different subtypes. Some of the true malignant lymphomas are associated with EBV infection, even in immunocompetent patients, such as Burkitt lymphoma, T-cell and NK-cell lymphomas, and Hodgkin lymphoma. However, the malignant lymphomas should clearly be separated from the other EBV-driven B-cell proliferations that occur in the post-transplant setting (true PTLD). These lymphomas probably arise due to continuous antigenic stimulation in a background of chronic immunosuppression, and appear to be increasing in incidence with better post-transplant treatment and prolonged follow-up.

A new classification of the lymphoproliferative disorders occurring after solid organ transplantation and allogeneic haematopoietic stem cell transplantation is proposed in Table I. True PTLD is a specific EBV-driven B-cell proliferation in this classification, and is the entity most likely to respond to reduced immunosuppression (RI) and/or rituximab immunotherapy, or new EBV-directed therapeutics. However, the aggressive non-Hodgkin lymphomas, whether EBV+ or EBV−, are unlikely to respond to RI or rituximab, and usually require aggressive chemotherapy. This is also true for Hodgkin lymphoma and plasma cell myeloma, whereas the indolent B-cell lymphomas may benefit from rituximab monotherapy. Although rare cases of EBV− diffuse large B-cell lymphoma (DLBCL) are reported to respond to RI (Nelson et al, 2000), such cases are anecdotal and need to be carefully studied. However, it should not be surprising that occasional cases of EBV− DLBCL do regress with RI, as the microenvironment plays an important role in lymphoma biology, but time is usually of the essence in treatment of this aggressive disease. The EBV− indolent plasma cell proliferations appear to respond well to RI (Perry et al, 2013), and EBV+ marginal zone B-cell lymphomas could also be given a trial of RI and/or rituximab. Adoption of this proposed classification in clinical practice will provide the basis for more rational therapeutic decisions and facilitate the development of well-designed clinical trials, as well as promote research into the epidemiology, pathogenesis and biology of this very heterogeneous group of disorders.

Author contributions

Dr. Weisenburger and Dr. Gross both drafted the paper and revised it critically, and approved of the submission and final version.

Conflict-of-interest disclosure

The authors declare no competing financial interests.

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The correspondence from Weisenburger & Gross is welcomed, as it stimulates discussion regarding further refinement of the current World Health Organization (WHO) classification system for post-transplant lymphoproliferative disorders (PTLD) (Swerdlow et al, 2008), to better reflect our current understanding of the heterogeneous entities within the different categories. However, we believe that it has little relevance to our study (Montanari et al, 2015), given that we reported a novel prognostic algorithm based on the extant classification of PTLD (Swerdlow et al, 2008).

In order to develop a meaningful classification system, we suggest a comprehensive review of the histopathological, immunophenotypic, genomic and clinical data generated thus far by experts in the field to determine relevant diagnostic criteria. The classification proposed by Weisenburger & Gross has merit, however the rationale behind some of the proposed categories (and terminology) is confusing. For example, it is unclear as to what entities are included in ‘Benign and reactive disorders, EBV− and polyclonal’ and why these should be differentiated from ‘True PTLD, always EBV+ (and polyclonal).’ It has been appreciated that cytomorphologically identical Epstein–Barr virus (EBV) positive or negative lymphoproliferations can occur post-transplantation, including florid follicular hyperplasia (FFH), reactive plasmacytic hyperplasia and polymorphic PTLD (P-PTLD), and biological differences between the EBV+ and EBV− proliferations are not apparent. Furthermore, how does one define clonality? A multitude of modalities have been used to establish the clonal nature of PTLD, including immune receptor gene rearrangement, viral integration and cytogenetic analyses. It is well known that these assays do not always yield the same result. For example cytogenetic analysis can detect clonal or oligoclonal populations in FFH, early lesions and P-PTLD that appear polyclonal by immunoglobulin gene rearrangement analysis (Vakiani et al, 2007). On the contrary, failure to detect clonal immune receptor gene rearrangements by polymerase chain reaction analysis is not always indicative of polyclonal proliferations, as mutations in the primer binding sites of immunoglobulin heavy or light chain genes in neoplastic B- or plasma cells can lead to false negative results.

How one would differentiate the monomorphic PTLD (M-PTLD) subtype of ‘true PTLD’ from ‘EBV+ malignant lymphoma’ is also not apparent, as currently M-PTLD are thought to represent either EBV+ (or EBV−) aggressive neoplasms, which are virtually always clonal and are subdivided into different subtypes, similar to B-cell non-Hodgkin lymphomas occurring in immunocompetent individuals, e.g. diffuse large B-cell lymphoma (DLBCL) and Burkitt lymphoma. It is our opinion that certain EBV negative lymphomas occurring in transplant recipients should be retained under the PTLD umbrella, as opposed to restricting the term ‘true PTLD’ to denote only EBV+ PTLD. Weisenburger and Gross point out that the incidence of EBV− PTLDs, especially DLBCL, increases with the duration of immunosuppression, which could be related to alterations in the microenvironment or other factors. Clinico-pathological studies and genomic analyses have also documented differences between EBV− PTLD (DLBCL) and DLBCL of immunocompetent hosts (Nelson et al, 2000; Rinaldi et al, 2010; Kwee et al, 2012; Morscio et al, 2013).

We believe that establishing more objective histopathological and phenotypic criteria that can reliably distinguish between the different types of PTLD is a worthwhile endeavour. Gene expression profile analysis has suggested that P-PTLD and M-PTLD (DLBCL) probably encompass heterogeneous entities (Vakiani et al, 2008). It is hoped that future transcriptomic and high-resolution genomic analyses of the neoplastic lymphocytes and tumour microenvironment will shed light into specific sub-entities within the different PTLD categories.

Knowledge of EBV infection should certainly encourage the use of novel EBV-directed therapeutic regimens, however a decision to reduce immunosuppression alone, as first line therapy, should not be based on this attribute. In keeping with the observations of our group and other investigators, the only prospective study of immunosuppression as first line therapy in adult PTLD by the Southwest Oncology Group