Diagnosis and Management of Posttransplant Lymphoproliferative Disorder in Solid-Organ Transplant Recipients

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The Epstein-Barr virus (EBV) has a pivotal pathophysiologic role in the development of most lymphoproliferative disorders that occur after solid-organ transplantation. The term “EBV-associated posttransplant lymphoproliferative disorder” (PTLD) includes all clinical syndromes of EBV-associated lymphoproliferation, ranging from uncomplicated posttransplant infectious mononucleosis to true malignancies that contain clonal chromosomal abnormalities. PTLDs are historically associated with a high mortality rate in patients who have a monoclonal form of the disorder. Recently described approaches to pathology, diagnosis, treatment, and preventive strategies of PTLD, however, have the potential to improve outcome.

Infection with Epstein-Barr virus (EBV) is believed to play a major pathophysiologic role in the development of most lymphoproliferative disorders that occur after solid-organ transplantation [1]. What is termed “EBV-associated posttransplant lymphoproliferative disorder” (PTLD) includes all clinical syndromes associated with EBV-driven lymphoproliferation, ranging from uncomplicated posttransplant infectious mononucleosis to true malignancies that contain clonal chromosomal abnormalities [2]. The diagnosis of PTLD historically has been associated with a mortality rate of ~50%–80% in patients who have a monoclonal form of the disorder [1, 3]. Recently described aggressive approaches to diagnosis and treatment of PTLD have the potential to improve outcome, however, as discussed below.

Primary EBV infection occurring after transplantation [4], cytomegalovirus (CMV) mismatch between donor and recipient [4], CMV disease [5], and the type and intensity of immunosuppression [4, 6–10] have all been identified as general risk factors for the development of this disorder in all solid-organ transplant recipients. Preliminary data have suggested that hepatitis C virus (HCV) infection and specific recipient cytokine gene polymorphisms may also be risk factors for PTLD development. Primary EBV infection is a powerful predisposing factor for early PTLD development. Several single-center analyses have found that EBV-seronegative patients experienced a 10–76-fold greater incidence of PTLD when compared with their seropositive counterparts [4, 9, 11, 12]. Because >90% of the population has immunity to EBV by the age of 40 years [11], primary EBV infection and EBV-associated PTLDs are of greater concern in pediatric solid-organ transplant programs. The incidence of PTLD also differs with the type of transplanted allograft, with a range of 0.7% in adult recipients of kidney transplants [13] to 32% in children with small-intestine transplants [14]. This may reflect not only differences in the immunosuppressive regimens used but also intrinsic biological differences between tissues.

Many of these risk factors have been most clearly defined for PTLD that occurs early after transplantation. PTLD occurring in the setting of primary EBV infection or associated with use of the immunosup-
The development of PTLD is influenced by the age of the recipient, the duration of immunosuppression, and the type of organ transplanted. Pretransplant EBV and CMV serostatus as risk factors for the development of late PTLD have not been extensively evaluated.

Because many of these factors are interrelated, a multivariate analysis would help to determine independent risk factors. This type of analysis, however, requires adequate numbers of patients from multiple transplant centers with standardization of diagnostic criteria (as described elsewhere [17]). In addition, the role of specific risk factor(s) or the time to the onset of PTLD in determining the response to prophylactic or therapeutic agents is unknown. For example, recent studies of PTLD in pediatric populations have reported lower mortality rates, in the range of 20%–40% [12, 18, 19]. Whether this reflects an improved outcome when PTLD occurs early after transplantation and/or in the setting of primary EBV remains to be determined through larger clinical studies.

Although much is known about the molecular mechanisms involved in EBV replication and latency, the specific mechanism(s) controlling virus reactivation in the immunocompromised host, and the relative role of lytic versus latent infection in the development of PTLD, are uncertain. Even in the presence of a strong humoral and cell-mediated immune response to the virus, EBV infection persists for the lifetime of the host [20]. Low-grade replication of EBV in B cells in the oropharynx can occur simultaneously with predominantly latent infection of B cells in peripheral blood and lymphoid tissue. EBV infection of B cells can also result in cellular activation and immortalization [21]. Reactivation of EBV and the proliferation of EBV-infected B cells are controlled by the immune response to the virus, particularly the human leukocyte antigen (HLA)–restricted EBV-specific cytotoxic T cell response [1]. When this response is inhibited by immunosuppressive therapy, the usual state of equilibrium between the virus and host immune response is disrupted in favor of the virus; latently infected cells can then either undergo proliferation or enter the lytic cycle.

De novo EBV infection can also be transmitted to the transplant recipient by donor organs or blood transfusions in this setting [22, 23]. In the past, it was believed that immunosuppression was associated with the expansion of EBV-infected proliferating lymphoblasts in the blood. Investigators have recently observed that the increase in EBV load observed in most transplant recipients is, surprisingly, the result of the expansion of latently infected resting, memory B cells rather than lymphoblasts. These authors also observed that, in some patients, replicating virus makes up a larger portion of the EBV burden than does the increased number of latently infected cells [24]. Although these observations require further validation, it is possible that the role of lytic EBV infection in the pathogenesis of PTLD may have been seriously underestimated.

Additional evidence that replicative EBV infection may be important in the development of PTLD includes the following: First, OKT3, which is associated with an increased risk for PTLD, can stimulate the production of inflammatory cytokines, which may contribute to EBV reactivation [25]. Second, the vast majority of lymphomas are of recipient lymphocyte, but donor virus, origin [26, 27], which indicates that the host’s cells are infected by virions from donor cells. Third, early studies suggested that polyclonal B cell proliferation may respond to antiviral therapy [28], which suggests that viral replication might play a role in PTLD in the absence of cytogenetic abnormalities and/or monoclonal proliferation. Finally, the presence of lytic virus infection can be demonstrated in ~40%–80% of lesions by detecting the linear form of the viral genome [29] or lytic cycle antigens [30–32] in a small proportion (usually <5%) of involved cells, usually with plasmacytoid differentiation.

A better understanding of the biology of EBV infection and the pathophysiology of posttransplant EBV-driven lymphoproliferation would result in a more rational approach to strategies for the prevention and treatment of this disorder. Specific issues that need to be addressed include the mechanism of EBV-induced cell transformation and virus reactivation from latency, the response of EBV-transformed B cells to physiologic stimuli, and further clarification of EBV-specific epitopes recognized by the immune system in vivo. Identification of cytokines or other stimuli (including other viruses) that may influence the lymphoproliferative process would also be useful. In the posttransplant setting in particular, it is important to obtain further validation of the phenotype of EBV-infected B cells responsible for the increased EBV load, as well as to determine EBV-specific genes expressed in these cells. Additional knowledge regarding the epidemiology of EBV infection after transplantation, including the role of virus burden, organ versus blood transfusion transmission, coinfection by other viruses (e.g., CMV and HCV), and superinfection with a second EBV strain, would also assist in the targeting of preventive strategies.

Published information currently allows for the development of specific recommendations for standardized diagnostic criteria for EBV-associated PTLD, which are discussed in the next section. In the absence of randomized, placebo-controlled trials, however, few data exist regarding the efficacy of specific treat-
ment or prophylactic protocols on which specific recommendations could be based. We therefore have summarized current knowledge of these therapies, providing guidelines for an approach to prophylaxis and treatment on the basis of published information.

**DIAGNOSIS OF PTLD**

The diagnosis and classification of PTLD are currently based on histologic criteria. Although the presence of certain other features, such as monoclonality, oncogene rearrangements, or mutations, may be more specific indicators of malignant transformation and prognosis, the techniques required for measurement of these parameters are not available in all centers. Future studies to determine the best indicator(s) of clinical outcome, including sensitivity to various treatments, may therefore require centralized pathology laboratory facilities for the performance of technically advanced assays.

Although serologic tests are readily available in most centers, they generally are not useful for the diagnosis of PTLD. In the immunocompetent host, primary EBV infections can be detected by seroconversion, with development of antiviral capsid antigen IgM and IgG antibodies and anti–early antigen and anti–Epstein-Barr nuclear antigen (EBNA) antibodies; however, transplant patients can fail to produce detectable anti-EBNA-1 antibodies in the setting of primary infection [33], and patients who are seropositive before transplantation can have falling anti-EBNA-1 titers associated with higher EBV loads and the development of PTLD [34, 35]. Although the presence of monoclonal or oligoclonal gammapathy may provide useful adjunctive evidence in cases of suspected PTLD [36], the specificity of this marker is also poor. Similarly, cytology has a limited role in PTLD diagnosis and should not be used to classify PTLD [37].

Pathologic examination of tissue is currently the gold standard for PTLD diagnosis (A-III). Although excisional biopsy is preferred, needle biopsy is acceptable when larger biopsies are impractical, as in the case of allograft organ biopsy. The tissue specimen should be interpreted by a hematopathologist or pathologist familiar with histopathologic features of PTLD and of allograft infection and rejection, and institutional protocols should be in place to ensure that tissue is handled appropriately for ancillary diagnostic tests (as described elsewhere [17]).

To facilitate interinstitutional comparisons of the epidemiology, prevention, and treatment of PTLD, it is essential that a standardized approach to the pathologic diagnosis of PTLD be used. In addition, the establishment of an international PTLD database that contains certain elements of standardized data would be helpful for designing future clinical trials. As much of the information described in the next section as is possible should be collected at each clinical center. These criteria are based on recommendations originally presented by Dr. M. Nalesnik at a Mayo Foundation–sponsored international consensus development meeting on EBV-induced PTLD in 1997 and included in a review by Paya et al. [17].

**Patient information.** Important clinical information that should be recorded for each patient includes the transplant recipient’s age, sex, and pretransplant EBV serostatus; the date and type of allograft for any and all transplants received; and the date of presentation with PTLD. Additional information that may prove useful for the design of preventive or prophylactic trials includes the dates, types, and doses of immunosuppression given; the dates and types of antiviral agents given; recipient CMV status; donor EBV and CMV serostatus; and EBV load, with specific details about the method and specimen type that were used to determine the virus load, if they are available.

Patient outcome should also be reported, including date(s) and type(s) of all therapies used and date of death (if applicable). The length of survival time should also be updated periodically for surviving patients, and the date of any disease recurrence should be noted. In addition, dates of any subsequent allograft transplants in PTLD patients should be provided, and follow-up outcome data should be reported as they become available.

**Staging of PTLD.** All organs known or suspected to be involved in PTLD and the evidence for their involvement (histologic, radiologic, and/or biochemical) should be recorded. The presence or absence of allograft involvement should also be explicitly stated for each case. Although no staging system currently exists for PTLD, it is recommended that the Ann Arbor staging classification system with Cotswold’s modifications that is used to stage non-Hodgkin’s lymphomas be applied to PTLD (including factors such as the presence or absence of symptoms, allograft, or CNS involvement), to provide a standardized reference system for the relationship of tumor burden to outcome.

**Histopathologic diagnosis.** If the term “posttransplant lymphoproliferative disorder” is to be used to describe the entire spectrum of lymphoproliferation occurring after transplantation, it is essential that reactive conditions such as infectious mononucleosis and plasma cell hyperplasia be clearly segregated in the classification process from potentially neoplastic lesions that contain monoclonal elements. Many of the classification systems that have been proposed are incorporated into the formulation of Harris et al. [38], which is recommended for use at the present time.

In addition to the morphologic classification, the following ancillary diagnostic tests are strongly recommended. The cell type of origin (B cell, T cell, null cell, or mixed) should be specified. The clonal status of the lymphoproliferation should also be mentioned, using the criteria listed in table 1, and the
Table 1. Criteria for determination of clonality in posttransplant lymphoproliferative disorder.

<table>
<thead>
<tr>
<th>Classification</th>
<th>Histopathologic findings</th>
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<tbody>
<tr>
<td>C0</td>
<td>No evidence of monoclonal component</td>
</tr>
<tr>
<td>C1</td>
<td>Minor clonal component estimated to comprise ≤50% of cells</td>
</tr>
<tr>
<td>C2</td>
<td>Monoclonal component estimated to comprise &gt;50% of cells</td>
</tr>
<tr>
<td>C3</td>
<td>Multiclonal or oligoclonal pattern</td>
</tr>
<tr>
<td>C4</td>
<td>Clonal pattern other than those listed above</td>
</tr>
<tr>
<td>Cx</td>
<td>Specimen inadequate for clonal determination or clonal determination not performed</td>
</tr>
</tbody>
</table>

The method used to determine clonality should be listed. The EBV status of the involved lymphocytes should be reported using the criteria listed in table 2. The method used to determine EBV involvement (detection of EBV-encoded RNA 2 by in situ hybridization, latent membrane protein 1 by immunostaining, or EBV DNA by PCR assay) [39, 40] should be specified.

Additional studies that would be of interest include determination of donor versus host origin of both virus isolates and involved lymphocytes, the presence of oncogene rearrangements or mutations, and the presence of CD20 (a potential therapy-associated marker). The techniques required for many of these determinations are not performed at all institutions, however, and these data may therefore not always be available.

Studies to determine optimal initial therapeutic approaches to PTLD would be greatly facilitated by all of the above information. The establishment of regional pathology laboratories would in turn facilitate the performance and standardization of these tests.

**PREVENTION OF PTLD**

In the absence of reliably effective therapy for all stages of PTLD, the optimal strategy for the management of PTLD in solid-organ transplant recipients is currently focused on prevention. The following recommendations address this issue.

Patients who are at high risk for the development of PTLD should be identified before transplantation (A-II). Because primary EBV infection is a significant risk factor for PTLD development, EBV serostatus should be determined for all potential transplant recipients. Patients who are also at risk for primary CMV infection or severe CMV disease should be identified because of their increased vulnerability to development of PTLD. In addition, children, recipients of small-bowel transplants, and patients who receive large doses of immunosuppression (especially OKT3) either for induction or allograft rejection should be considered to be at high risk for PTLD. Such patients should be monitored carefully for clinical evidence of EBV infection, including careful review of their allograft biopsies for evidence of early lymphoproliferative disease.

Aggressive supplemental immunosuppression should be used only in the presence of biopsy-proven acute rejection (A-II). Because PTLD frequently presents with allograft dysfunction, it is important to make a pathologic diagnosis of rejection by use of standardized criteria and to clearly distinguish early PTLD from rejection before more potent antirejection therapy is started. Sensitive techniques to identify EBV-infected cells in tissues, including in situ hybridization and PCR, are particularly useful in this setting. Patients receiving prolonged or repetitive courses of antilymphocyte globulin should be included in the patient group targeted for increased surveillance for PTLD.

Antiviral agents with activity against EBV may be of benefit as prophylaxis for the prevention of PTLD (C-III). Lytic virus infection may be important in early increases in EBV load observed after transplantation and the polyclonal lymphoproliferation associated with infectious mononucleosis and B cell hyperplasia. Because CMV disease is a cofactor in PTLD development and because ganciclovir has greater activity against EBV in vitro [41], the use of ganciclovir may be preferable to acyclovir use. Historical comparisons of the incidence of PTLD in patients receiving and not receiving acyclovir and/or ganciclovir prophylaxis, either immediately after transplantation or during antilymphocyte antibody therapy for acute rejection, suggest that either prophylactic antiviral drug may be of some benefit [10, 42, 43]; however, PTLD has also been documented in patients receiving ganciclovir and/or acyclovir prophylaxis. Similarly, the role of passive administration of neutralizing antibodies to EBV through iv immunoglobulin therapy is not clear, although results in the animal model of PTLD are promising [44]. It is clear that prospective, placebo-controlled trials of any of these forms of antiviral prophylaxis for PTLD are needed. Stratification of patients in these trials into groups, based on age and risk status (e.g., high risk associated with primary EBV infection or use of OKT3 for induction), would be helpful. Several such trials examining the usefulness of prophylactic passive immunization by use of iv immunoglobulin products for the prevention of PTLD in pediatric transplant populations are currently in progress [45] (M. Green, personal communication).

Table 2. Criteria for determination of Epstein-Barr virus (EBV) status in posttransplant lymphoproliferative disorder.

<table>
<thead>
<tr>
<th>Classification</th>
<th>Histopathologic findings</th>
</tr>
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<tbody>
<tr>
<td>E0</td>
<td>No evidence of EBV</td>
</tr>
<tr>
<td>E1</td>
<td>EBV present; not further categorized</td>
</tr>
<tr>
<td>E2</td>
<td>EBV present; no clonal component seen</td>
</tr>
<tr>
<td>E3</td>
<td>EBV present; monoclonal component seen</td>
</tr>
<tr>
<td>Ex</td>
<td>Specimen inadequate or no procedures performed to determine presence or absence of EBV</td>
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The monitoring of EBV load in patients who are at high risk for PTLD is a promising technique that would permit preemptive treatment in the form of reduction of immunosuppression and/or the use of antiviral agents (C-II). Several groups have demonstrated an association between high EBV loads and PTLD [46–52]. Moreover, high virus loads antedate the presentation of clinical PTLD. There is, however, a clear need to standardize monitoring techniques. EBV loads in transplant recipients have been assayed using peripheral blood lymphocytes [50], whole blood [51], and serum [52]. The relationship between virus loads measured in each compartment, the relative contribution of lytic versus latent infection to the virus load assayed, and the sampling site and virologic assays that are most predictive of PTLD remain uncertain. Additional studies of the natural history of EBV load after transplantation and its relationship to PTLD would help to define “trigger points” that are predictive of PTLD development and at which preemptive intervention should take place [53, 54].

Overall, PTLD reportedly affects the transplanted allograft in ~30% of patients [11, 55, 56], although early-onset PTLD may be more highly associated with allograft involvement [11]. An additional approach to patient monitoring might therefore consist of identifying and quantifying EBV-infected cells in biopsies performed for any reason in high-risk patients [57–59]. Prospective studies are needed to determine whether the presence of a certain amount or increasing number of EBV-positive cells is associated with subsequent development of PTLD.

**TREATMENT OF PTLD**

Approaches to the management of patients with PTLD have often been based on clinical outcomes described in case reports or a limited series of patients. No controlled trials with therapeutic intervention have been performed. Furthermore, spontaneous regression of PTLD after solid-organ transplantation occurs in many patients after a reduction in immunosuppression. Because most patients receive other therapies concomitant with a reduction in immunosuppression, it is difficult to evaluate the true efficacy of individual therapeutic approaches; however, case reports that indicate efficacy of specific agents without a reduction in immunosuppression have been published [60].

Our recommendations focus on the management of EBV-associated PTLD occurring within the first year after transplantation. These strategies may have limited application in the setting of PTLD that occurs after that time and/or in EBV-negative or T cell tumors.

The most important initial strategy in the management of PTLD is to reduce and even to discontinue immunosuppressive therapy, if possible (A-II), with regression evident in 23%–50% of patients as a result (including both monoclonal and polyclonal lesions) [60–64]. It is important to note that none of the following parameters—pretransplant EBV serostatus, clinical presentation, extent of disease, or pathologic features—can definitively predict whether the patient will respond to a reduction in immunosuppression. EBV load at the time of PTLD diagnosis has not been explored as a variable that might predict response. How should immunosuppression be reduced? Should it be withdrawn or reduced in a stepwise manner? This is of particular concern in patients who have undergone transplantation of vital organs. There are limited data to suggest that high EBV loads are immunosuppressive, and rejection events are highly unlikely if the patient’s virus load remains above specific levels [53] (S. Weber, personal communication). Although virus load monitoring may allow immunosuppression to be more safely withdrawn or reduced, these observations must be further validated. In clinical trials evaluating PTLD treatment, in which reduction of exogenous immunosuppression is an initial step, it is important that clear protocols for implementing this step be established. The kinetics of PTLD regression are poorly defined; how long one should wait before proceeding to further immunosuppression and/or alternative therapeutic interventions is not known. Allograft function and other markers for rejection must be monitored closely after a reduction in immunosuppression. EBV load monitoring may be also be useful after the response to reduction of immunosuppression or other treatments is seen [65–67], and EBV load can serve as an early surrogate marker for relapse of disease. Specific virus load levels at which additional therapeutic steps should be initiated are unknown, however, and routine use of virus load monitoring cannot yet be recommended.

As an adjunctive therapy to immunosuppression reduction, surgical resection appears to be useful for treatment of isolated PTLD lesions, for tumor debulking, or for management of local complications such as gastrointestinal hemorrhage or perforation [19, 68]. Local radiotherapy may also be useful for such lesions, particularly when they occur in the CNS (see below) (B-II). In several studies, the use of surgical excision or radiotherapy alone for the management of localized disease after the reduction of immunosuppression has resulted in durable responses and low patient mortality rates, which suggests that this approach should be considered early in patient management, when feasible [18, 69].

A secondary approach to treatment of EBV-associated PTLD often consists of the administration of antiviral drugs, immunoglobulin therapy, and/or IFN-α (C-III). Antiviral therapy in the form of both acyclovir and ganciclovir has been used in the management of PTLD, either alone or in combination with immunoglobulin [27, 70, 71]. In anecdotal cases, PTLD has been shown to respond to acyclovir therapy that is not accompanied by reduction of immunosuppression [28]; however, although lytic EBV infection is known to be present during PTLD [29–32], and lytic viral replication is presumably responsible
for polyclonal B cell proliferation [32], established PTLD lesions appear to be composed largely of latently infected B cells, which should not be sensitive to antiviral drugs. Antiviral medications generally may still be helpful to prevent recruitment of B cells to the lymphoproliferative process, especially during the early phases of PTLD development. Similarly, immunoglobulin preparations may prevent new infection of cells and/or contribute to antibody-dependent cell-mediated cytotoxicity. Furthermore, these agents may also modify the effect of other herpesviruses, such as CMV, on the lymphoproliferative process. As with the use of these agents for prophylaxis, their use for treatment of PTLD needs to be assessed prospectively in randomized, placebo-controlled trials.

IFN-α has both antiviral and antiproliferative activity and has the added advantage of affecting the host immune response via its activity as a T-helper cell type 1–associated cytokine (C-III) [72]. The association of T-helper cell type 2 cytokine responses with PTLD, and their disappearance after PTLD resolution, lends support to the use of IFN-α for treatment of this disorder [73]. Indeed, circulating IL-4 and IL-10 levels both appear to be useful for monitoring PTLD and response to therapy, although specific levels at which therapeutic intervention is appropriate still need to be determined [74, 75]. Experience with use of IFN-α for the treatment of PTLD is most extensive in bone marrow transplant recipients [76], but the limited data on solid-organ transplant recipients indicate that the majority of patients may respond to IFN-α in conjunction with a reduction in immunosuppression [77, 78]. Interferon therapy is associated with a theoretical risk of precipitating rejection, because it can up-regulate HLA expression in the renal allograft [79, 80]; however, whether this has any clinical relevance in recipients of other solid-organ allografts or in the setting of profound immunosuppression in patients with PTLD is uncertain. Limited data from one prospective study indicate that 4 of 14 patients treated with IFN-α (29%) may develop rejection during therapy, which is readily treatable [69].

Monoclonal anti–B cell antibodies against CD21 and CD24 have also been used for the treatment of PTLD [81–84]. Benkerrou et al. [82] recently published the results of an open multicenter trial evaluating the efficacy of these monoclonal antibodies in patients with PTLD; however, many of the patients treated with these agents had received concomitant or recent therapy with acyclovir, ganciclovir, interferon, or steroids in association with a reduction in immunosuppression. Nonetheless, 20 of 31 solid-organ transplant recipients (65%) achieved complete remission, and only 1 of those 20 patients (5%) relapsed. Predictive factors for treatment failure included multi-visceral disease, monoclonality, CNS disease, and late-onset PTLD. Failure of treatment associated with defective expression of both CD21 and CD24 on the surface of proliferating B lymphocytes has also been reported [84].

Unfortunately, anti-CD21 and -CD24 antibodies are no longer commercially available. An anti-CD20 antibody preparation (rituximab) approved for use in relapsed low-grade non-Hodgkin’s lymphoma is currently being tested in patients with PTLD refractory to reduction of immunosuppression. Ancendotal reports of the efficacy of this monoclonal antibody in PTLD have been published [85–88]. The low toxicity and high specificity associated with the use of anti-CD20 make it very attractive as a first-line agent for therapy of PTLD after reduction of immunosuppression; however, further data regarding its efficacy are required.

Lesions in the CNS often fail therapy and tend to relapse. This suggests that the CNS is an immunologically privileged site, and special intervention may be necessary in these cases. Approaches that have shown some usefulness in anecdotal reports include local radiotherapy or intrathecal administration of anti–B cell antibodies in conjunction with IFN-α [89, 90]; such approaches should be considered once CNS involvement is documented (B-III).

Because of the associated risk of neutropenia and septic complications, standard cytotoxic chemotherapy is rarely used as a first- or second-line therapy for early PTLD, but it is frequently used in patients who have failed the more conservative approaches to treatment outlined above (D-III) [61, 69, 91–94]. Anthracycline-based regimens have been noted to achieve a remission rate as high as 69% among patients with B cell tumors. Despite these good response rates, patient mortality rates can remain unacceptably high. Many of these patients recover from PTLD but succumb to complications related to chronic rejection and sepsis. Improvement in these results may be possible through better management of immunosuppression during chemotherapy and augmentation of antimicrobial prophylactic strategies. An alternate approach is currently being evaluated that involves the use of modified, less intense chemotherapy regimens that simultaneously provide an antirejection effect [95].

Immunomodulation and adoptive immunotherapy have also been used for the management of PTLD. Limited data on solid-organ transplant recipients have shown regression of disease and/or decreased levels of EBV DNA after adoptive transfer of autologous EBV-specific cytotoxic T lymphocytes [96, 97]. The development of banks of cloned EBV-specific cytotoxic lymphocytes for use in the treatment of PTLD based on a best HLA match has also been proposed [45]. Although autologous lymphokine-activated killer cells appear to be effective against experimental PTLD in a mouse model with severe combined immunodeficiency [98], their use for the treatment of refractory PTLD in solid-organ transplant recipients has demonstrated equivocal efficacy to date [99]. Alternative immunomodulatory approaches include the use of anti-IL-6 antibodies, but currently available data using this approach are limited to patients with myeloma [100].
RETRANSPLANTATION AFTER PTLD

Successful transplantation in allograft recipients who have recovered from PTLD is possible (A–III), and reported long-term follow-up of ≤5 years indicates no evidence of PTLD recurrence in some patients [101–104]. It is reasonable to assume that patients in whom PTLD was clearly associated with primary EBV infection would be at significantly lower risk of recurrent EBV-associated PTLD if they have remained free of disease for a significant interval and an immune response to the initial EBV infection has occurred. The development of PTLD associated with recurrent EBV infection should be considered to result from profound immunosuppression; in any patient with recurrent EBV infection and PTLD who receives another allograft, immunosuppression should be minimized as much as possible.

CONCLUSIONS

Additional knowledge concerning the mechanism(s) of EBV-induced B cell transformation and reactivation of lytic virus from latency is necessary to understand the role of latent versus lytic virus in the development of PTLD. Because no reliably effective therapy has been found for this disease, the current optimal strategy for the management of PTLD in solid-organ transplant recipients is prevention. Prophylactic therapies, including antiviral agents and immunoglobulins, need to be tested in randomized, placebo-controlled trials to determine their true efficacy. Although anecdotal evidence suggests that certain treatments may be useful for this disease, they also need to be tested in a randomized, controlled manner. Agreement regarding standardized therapeutic protocols that can be tested in a multicenter trial format, using patients whose lesions have been stratified by use of standardized approaches to histopathology and virology, would be an important first step to improving therapeutic approaches to PTLD.

Acknowledgment

We thank Dr. J. Fishman for assistance in reviewing the manuscript.

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