The biology and treatment of plasmablastic lymphoma

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Plasmablastic lymphoma (PBL) is an aggressive lymphoma commonly associated with HIV infection. However, PBL can also be seen in patients with other immunodeficiencies as well as in immunocompetent individuals. Because of its distinct clinical and pathological features, such as lack of expression of CD20, plasmablastic morphology, and clinical course characterized by early relapses and subsequent chemotherapy resistance, PBL can represent a diagnostic and therapeutic challenge for pathologists and clinicians alike. Despite the recent advances in the therapy of HIV-associated and aggressive lymphomas, patients with PBL for the most part have poor outcomes. The objectives of this review are to summarize the current knowledge on the epidemiology, biology, clinical and pathological characteristics, differential diagnosis, therapy, prognostic factors, outcomes, and potential novel therapeutic approaches in patients with PBL and also to increase the awareness toward PBL in the medical community.

Methods

To provide the most detailed background information on PBL, we conducted an extensive literature search by looking for articles in any language using PubMed/Medline, EMBASE, and Google Scholar published from January 1997 through October 2014. The main search terms used were “plasmablastic lymphoma” and “PBL.” Each article was acquired in full, and reference articles were examined in an effort to eliminate previously included cases. Our search included all cases of PBL diagnosed according to the World Health Organization classification and with relevant clinicopathological information. We excluded reviews and laboratory experiments without original cases, unpublished abstracts, and cases associated with human herpesvirus 8 (HHV-8) or large B-cell lymphoma arising in HHV-8-associated multicentric Castleman disease (MCD).

Our initial search rendered 612 articles. The number of PBL publications has increased in recent years, which could be a reflection of an increasing awareness of PBL among clinicians and pathologists. In effect, 320 articles were published between 1997 and 2009 (13 years), and 292 articles have been published since 2010 (<5 years). After reviewing the full-text articles, 177 were selected, and data from 590 individual cases of PBL were collected and analyzed.

Epidemiology

The incidence of HIV-associated PBL has been estimated at approximately 2% of all HIV-related lymphomas.9 In addition to a strong association with HIV infection,1,1 PBL has also been reported in patients with other causes of immunodeficiency such as iatrogenic immunosuppression in the context of solid organ transplantation or in elderly patients.4,10 Cases of HIV-negative PBL may also arise from previously existing lymphoproliferative or autoimmune disorders.4,11 A number of cases have been described in otherwise immunocompetent patients.11 However, the actual incidence of both HIV-positive and HIV-negative PBL is unknown.

On the basis of our review of 590 cases, PBL has been reported in patients of all ages (range, age 1 to 90 years), although with only a minority of pediatric cases described to date. The sex distribution in PBL cases shows a male predominance (75%).

Pathogenesis and cell of origin

One of the most important functions of the germinal center (GC) reaction is to produce clones of B cells with the highest affinity against a specific antigen.12 Within the GC, B-cell clones migrate from the “light zone” to the “dark zone” and vice versa, outcompeting each other not only for the limited amounts of antigen presented by follicular dendritic cells but also for survival signals from helper T-cells (Figure 1, upper panel). B-cell clones acquire somatic mutations (ie, somatic hypermutation) as a mechanism of affinity maturation.13 In addition, B-cell
clones undergo DNA class switching recombination to immunoglobulin A (IgA), IgE, or IgG, increasing antibody diversity. Autoimmune or anergic B-cell clones are deemed to undergo apoptosis. As expected, a large proportion of B cells will undergo apoptosis during the GC reaction. Apoptosis in the GC can be triggered by B-cell receptor (BCR), T-cell growth factor β (TGF-β), or Fas-mediated processes. Both BCR and TGF-β signaling induce apoptosis via activation of proapoptotic members of the BCL-2 family resulting in an increase in BH3-only proteins and loss of BCL-XL, which leads to mitochondrial depolarization and intrinsic apoptosis. Rarely, GC B cells undergo apoptosis via FAS. The FAS death induction signaling complex is naturally inactive but gets activated by the lack of survival signaling from T cells and follicular dendritic cells, inducing activation of caspase 8 with subsequent extrinsic apoptosis. The fate of selected GC B lymphocytes is long-lived memory lymphocytes or plasma cells. A subset of lymphocytes become plasma cells through stochastic mechanisms, without the need for antigenic stimulation. Signaling that leads to plasma cell differentiation involves inactivation of PAX-5 and BCL-6 transcription factors through the plasma cell transcription factor BLIMP-1. Morphologically, centrocytes transform to plasmablasts before becoming mature plasma cells, and phenotypically, cells express CD38, interferon regulatory factor 4/multiple myeloma 1 (IRF-4/MUM-1), and lose CD20 while maintaining CD19 expression. The cell of origin in PBL is thought to be the plasmablast, an activated B cell that has undergone somatic hypermutation and class switching recombination and is in the process of becoming a plasma cell. The presence of plasmablasts is noted in reactive processes associated with viral infections such as Epstein-Barr virus (EBV), and HIV among others. The pathogenesis of PBL is incompletely understood.
understood; however, recent studies have identified the presence of MYC gene rearrangements in addition to the association with EBV infection as important pathogenic mechanisms.

PBL is associated with EBV infection, and EBV infection is associated with prevention of apoptosis in B cells by several mechanisms related to EBV antigens (Figure 1, left lower panel). LMP-1, which mimics constitutively active CD40 and provides the necessary T-cell–like survival help, signals through nuclear factor κB (NF-κB) inducing the expression of FLIP and protects B cells from FAS-mediated apoptosis. LMP-2A mimics the function of the BCR by associating with Syk and Src, protecting infected B cells from BCR-mediated apoptosis. Preventing apoptosis through modulation of the TGF-β pathway allows MYC to overcome the regulatory effects of BCL-6 or BLIMP-1. A less well-understood function of MYC is also the induction of apoptosis. Preventing apoptosis through modulation of the TGF-β pathway allows MYC to overcome the regulatory effects of BCL-6 or BLIMP-1. A less well-understood function of MYC is also the induction of apoptosis. Preventing apoptosis through modulation of the TGF-β pathway allows MYC to overcome the regulatory effects of BCL-6 or BLIMP-1. A less well-understood function of MYC is also the induction of apoptosis.
Eighteen cases were HIV-positive and 3 were HIV-negative. More than 80% of pediatric PBL cases presented with advanced stage. The oral cavity (33%) was the most common site of involvement.

**Pathological features**

PBL is a high-grade neoplasm with cytomorphic features such as large immunoblasts or large plasma cells that express plasma cell markers and lack B-cell markers. The diagnosis can be challenging because the tumor cells may be indistinguishable from plasmablastic myeloma or from lymphomas with plasmablastic morphology. The tumor has a diffuse growth pattern, and it effaces the architecture of extranodal or nodal sites. A “starry-sky” pattern, with frequent tingible body macrophages, is common. The neoplastic cells are large with abundant cytoplasm and central oval vesicular nuclei with prominent nucleoli as noted in large immunoblasts. When PBL occurs in the oral mucosa of HIV-positive patients, the neoplastic cells appear as large centroblasts and/or immunoblasts (Figure 2A), whereas a more apparent plasma cell differentiation with basophilic cytoplasm, paranuclear hof, and eccentric large nuclei (Figure 2B) occurs more in extranodal sites different from the oral mucosa in HIV-negative patients. Necrosis, karyorrhexis, and increased mitotic figures are common.

The immunophenotype is similar to that in plasma cell neoplasms, positive for CD79a, IRF-4/MUM-1, BLIMP-1, CD38, and CD138. The neoplastic cells are negative for B-cell markers CD19, CD20, and PAX-5; however, a subset may be dim positive for CD45. Some cases express T-cell markers CD2 or CD4. Immunohistochemistry with the antibody MIB-1, which detects the proliferation marker Ki-67, shows that most or all neoplastic cells are positive. MYC was more commonly seen in HIV-positive patients (75%) and in patients with AIDS. In a recent study, EBV infection based on EBER expression, which is the most sensitive methodology for detecting EBV infection within the architecture of extranodal or nodal sites, was observed.2

**Molecular genetic testing**

Molecular genetic testing reveals that about two-thirds of cases have MYC rearrangements, and a minor subset have MYC amplification. Comparative genomic hybridization shows that PBL is genomically more closely related to DLBCL than to myeloma. The main differential diagnosis of PBL is plasmablastic or anaplastic multiple myeloma that may be morphologically and immunophenotypically identical to PBL. Features that favor PBL include association with HIV infection and EBER positivity in neoplastic cells. Features favoring myeloma include the presence of monoclonal paraproteinemia, hypercalcemia, renal dysfunction, and lytic bone lesions. However, the distinction may be impossible and is clearly arbitrary in rare cases. The median age of PBL patients without underlying immunodeficiency is 64 years, which coupled with their frequent association with EBV infection, overlaps with EBV-positive DLBCL of the elderly, which is usually CD20⁺/CD79a⁻/CD138⁻. Primary effusion lymphoma usually manifests as pleural or pericardial effusion and rarely associates with lymphadenopathy or mass, but it shows a strong association with HHV-8. Plasmablastic microlymphoma arising in MCD can be distinguished by recognizing underlying MCD. IgA or IgG λ light chain restriction and strong association with HHV-8. Anaplastic lymphoma kinase (ALK)-positive DLBCL is considered to arise from unmutated IgM-expressing B cells and shows plasmablasts that express CD138 and IRF-4/MUM-1 and lack PAX-5 and CD20. The expression of ALK usually results from t(2;17)(p23;q23) in which ALK partners with CC1. DLBCL associated with chronic inflammation is associated with EBV infection and usually involves body cavities or narrow spaces. The latency period between chronic inflammation and the development of the lymphoma is more than 10 years. Localized tumors associated with medical devices or associated with cardiac myxomas are included in this table.

**Table 2. Selected pathological features of PBL (literature review from 1997 to 2014)**

<table>
<thead>
<tr>
<th>Feature</th>
<th>All cases</th>
<th>HIV-positive</th>
<th>HIV-negative</th>
<th>Posttransplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunophenotype</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD10</td>
<td>20%</td>
<td>32%</td>
<td>15%</td>
<td>0%</td>
</tr>
<tr>
<td>CD20</td>
<td>Low</td>
<td>8%</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>CD30</td>
<td>Subset</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD45</td>
<td>Low</td>
<td>31%</td>
<td>33%</td>
<td>70%</td>
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<tr>
<td>CD56</td>
<td>25%</td>
<td>27%</td>
<td>22%</td>
<td>42%</td>
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<td>CD79a</td>
<td>Common</td>
<td>45%</td>
<td>36%</td>
<td>68%</td>
</tr>
<tr>
<td>CD138</td>
<td>90%</td>
<td>94%</td>
<td>87%</td>
<td>88%</td>
</tr>
<tr>
<td>ALK-1</td>
<td>0%</td>
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<td></td>
<td></td>
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<tr>
<td>BCL-2</td>
<td>Uncommon</td>
<td></td>
<td></td>
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<tr>
<td>BCL-6</td>
<td>Negative</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMA</td>
<td>Common</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HHV-8</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
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<tr>
<td>IRF-4/MUM-1</td>
<td>~100%</td>
<td>~100%</td>
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<td>100%</td>
</tr>
<tr>
<td>EBV LMP-1</td>
<td>Uncommon</td>
<td>Occasional</td>
<td>Occasional</td>
<td></td>
</tr>
<tr>
<td>EBNA-2</td>
<td>Negative</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>EBV latency pattern</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Cytoplasm Ig</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MIB-1/Ki-67</td>
<td>High</td>
<td>90%</td>
<td>83%</td>
<td>88%</td>
</tr>
<tr>
<td>PAX-5</td>
<td>Negative</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MYC</td>
<td>~50%</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>TP53</td>
<td>~50%</td>
<td>67%</td>
<td>8%</td>
<td></td>
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<tr>
<td>Molecular testing</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>BCL-2 GR</td>
<td>Negative</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCL-6 GR</td>
<td>Negative</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EBER</td>
<td>66%</td>
<td>75%</td>
<td>50%</td>
<td>67%</td>
</tr>
<tr>
<td>IgH GR</td>
<td>Monoclonal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MYC GR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>amplifications</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>TCR GR</td>
<td>Polyclonal</td>
<td></td>
<td></td>
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<tr>
<td>Gene profile</td>
<td></td>
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</tr>
<tr>
<td>Segmental gains:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1p36.11-1p36.33</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1q21.1-1q23.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1p36.11-1p36.33</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALK-1, anaplastic lymphoma kinase 1; EBNA-2, EBV nuclear antigen 2; EMA, epithelial membrane antigen; GR, gene rearrangement; IRF-4/MUM-1, interferon regulatory factor 4/multiple myeloma 1; LMP-1, latent membrane protein 1; TCR, T-cell receptor.</td>
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</tbody>
</table>
Similar poor outcomes were seen among 50 HIV-positive PBL patients who received combined antiretroviral therapy (cART). This was a multicenter, retrospective case series from 13 institutions that reported a median OS of 11 months and a 5-year OS rate of 24%. A German study from 30 centers that included 18 HIV-positive patients with PBL treated after 2005 reported a median OS of 5 months. The AIDS Malignancy Consortium presented data in abstract form from 9 centers that included 19 HIV-positive patients treated after 1999; the 1-year OS rate was 67%. Although encouraging, it is difficult to draw firm conclusions given the preliminary nature of the report. An Italian study showed 3-year OS of 67% in 13 HIV-positive PBL patients treated with cART. The reasons for the better outcome are unclear, although the patients had a CD4 count >0.2 × 10⁹/L. Comparative studies showed that HIV status did not appear to affect outcomes in PBL. However, there was a suggestion that immunosuppression among HIV-negative patients was associated with worse outcomes.

The International Prognostic Index (IPI) scoring system is the most commonly used risk stratification tool for aggressive lymphomas, and it includes age, performance status, lactate dehydrogenase (LDH) levels, number of extranodal sites, and clinical stage to prognosticate survival. A series of retrospective studies have shown that the IPI score has prognostic value in patients with PBL. However, the prognostic value of the IPI score in PBL appears to heavily rely on advanced stage and poor performance status as indicators of worse outcome. Age, LDH levels, and bone marrow involvement did not appear to affect outcomes in a retrospective case series; however, age and LDH levels were associated with adverse outcomes in another study.

The prognostic value of EBV-related antigens expression in PBL cases is unclear. Some studies have shown that EBV expression is not associated with outcome in HIV-associated PBL. However, other studies have associated EBV with a better outcome in immunocompetent patients with PBL. Of note, EBV expression is commonly determined by the expression of EBER in the malignant cells. EBER is not a quantitative test, however, and does not allow stratifying subsets of infection. More recently, the presence of MYC gene rearrangements has been shown to be associated with shorter OS time in patients with PBL. In a systematic review that assessed 57 patients with PBL in whom MYC status was evaluated, patients with MYC gains or translocations had a worse OS than patients with a normal MYC. Specifically in HIV-positive patients with PBL, MYC gene rearrangements were associated with a sixfold increased risk of dying from any cause.

The expression of CD20 or CD45 has not been associated with outcomes in patients with PBL. Conversely, a series of studies have suggested a worse outcome in patients with Ki-67 expression >80%. A smaller study did not show prognostic value for Ki-67 expression. In HIV-associated PBL, CD4 counts <0.2 × 10⁹/L were not associated with worse OS but appeared to associate with shorter progression-free survival time.

Table 3. Differential diagnosis of PBL

<table>
<thead>
<tr>
<th>Disease distribution</th>
<th>PBL</th>
<th>Plasmablastic myeloma</th>
<th>LBCL</th>
<th>HHV-8-positive</th>
<th>IBL</th>
<th>DBLBC</th>
<th>ALK-positive</th>
<th>DBLCL</th>
<th>DLBCL</th>
<th>ACI</th>
<th>PEL</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV infection</td>
<td>~70%</td>
<td>No</td>
<td>Nodal</td>
<td>Nodal</td>
<td>Nodal</td>
<td>Nodal</td>
<td>Extranodal</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Pathogenesis</td>
<td>EBV, HIV, IL-10</td>
<td>IL-6</td>
<td>HHV-8, MCD</td>
<td>ALK</td>
<td>EBV, IL-10,</td>
<td>IL-6</td>
<td>HHV-8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive markers</td>
<td>CD138, IRF-4/MUM-1, MYC</td>
<td>CD138, cytoplasmic Ig, MYC</td>
<td>CD20&lt;sup&gt;+&lt;/sup&gt;, CD138&lt;sup&gt;+&lt;/sup&gt;, IgM</td>
<td>CD20, CD4, CD45</td>
<td>ALK, CD4, CD45</td>
<td>CD20, CD4, IRF-4/MUM-1, CD30&lt;sup&gt;+&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative markers</td>
<td>CD20, PAX-5</td>
<td>CD20, PAX-5, BCL-6</td>
<td>CD138</td>
<td>CD4, CD138</td>
<td>CD20, CD30, MYC</td>
<td>ALK, PAX-5, CD20, CD138, Ig</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Proliferation rate</td>
<td>&gt;90%</td>
<td>&gt;90%</td>
<td>&gt;90%</td>
<td>&gt;90%</td>
<td>&gt;80%</td>
<td>&gt;90%</td>
<td>&gt;90%</td>
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<tr>
<td>Cytoplasmic</td>
<td>50%-70%</td>
<td>&gt;90%</td>
<td>IgA λ</td>
<td>Uncommon</td>
<td>Uncommon</td>
<td>Uncommon</td>
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<tr>
<td>immunoglobulin</td>
<td>EBV infection</td>
<td>Common</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Common</td>
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<tr>
<td>EBV latency pattern</td>
<td>I</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>III</td>
<td>I</td>
<td></td>
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<tr>
<td>HHV-8 infection</td>
<td>No</td>
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<td>No</td>
<td>Yes</td>
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<tr>
<td>Molecular genetics</td>
<td>MYC GR</td>
<td>Myeloma FISH</td>
<td>Unmutated Ig</td>
<td>MYC GR</td>
<td>t(2;17)(p23;q23)</td>
<td>TP53 mutations</td>
<td>Hypermutated</td>
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</tbody>
</table>

ACI, associated with chronic inflammation; ALK, anaplastic lymphoma kinase; FISH, fluorescence in situ hybridization; GR, gene rearrangement; IBL, immunoblastic; IL, interleukin; IRF-4/MUM-1, interferon regulatory factor 4/multiple myeloma 1; LBCL, large B-cell lymphoma; NA, not available; PEL, primary effusion lymphoma.
Current treatment options and emerging therapies

The outcome of untreated patients with PBL is dismal, with a median OS of 3 months for HIV-positive patients and 4 months for HIV-negative patients.2 Conversely, HIV-positive patients with PBL who attain a complete remission after autologous transplantation with a current OS rate of 34% (92% 3-year OS) and 4 patients after initiation of cART was noted in two case reports of HIV-positive patients.45,46 Similarly, regression of PBL after decreasing dose of methotrexate was noted in an HIV-negative patient with rheumatoid arthritis.47

Given the dismal prognosis of patients with PBL, we can argue that there is no standard of care for patients with PBL. In particular, the use of cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) is considered inadequate therapy, and current guidelines recommend more intensive regimens.48 Such regimens include infusional etoposide, vincristine and doxorubicin with bolus cyclophosphamide and prednisone (EPOCH),49 cyclophosphamide, vincristine, doxorubicin, methotrexate alternating with ifosfamide, etoposide, and cytarabine (CODOX-M/IVAC),50 or hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with methotrexate and cytarabine (hyper-CVAD).51 However, two studies of patients with PBL treated with chemotherapy regimens more intensive than CHOP did not identify a survival benefit.3,44 A patient-level meta-analysis identified a survival benefit of using EPOCH over CHOP in patients with HIV-associated lymphomas.52,53 It is unclear, however, whether any patients with PBL were included in this analysis. Importantly, two prospective studies are evaluating the safety and efficacy of infusional EPOCH in patients with high-risk DLBCL, including PBL (NCT0102182 and CTSU9177).

Only a handful of cases have reported the use of intrathecal agents to minimize the risk of central nervous system involvement. However, given the high proliferation rate of PBL, the strong association with HIV infection, the high rate of extranodal involvement, and the presence of MYC translocations, we believe that intrathecal prophylaxis should be considered in most patients with PBL. The improved outcomes of cART among patients with HIV-associated DLBCL have not been readily apparent among patients with HIV-associated PBL. Two studies suggested that HIV-positive patients with PBL who also received cART had improved survival,11,14 whereas another study did not.23 The information on radiotherapy is rather scant. Radiotherapy has been used as part of treatment in approximately 20 to 30 PBL cases from the literature, but no conclusion can be made from this limited experience. More recently, the role of stem cell transplantation (SCT) in patients with PBL has been assessed.54 It appears that patients with PBL with chemotherapy-sensitive disease might benefit from autologous SCT in first remission. A recent study reported that 5 HIV-positive patients with PBL who received high-dose chemotherapy (HDC) followed by autologous SCT in first remission achieved prolonged OS times.83 Similarly, a case series of 9 HIV-negative patients with PBL reported encouraging results with a 5-year OS of 58%.55 In that study, 4 patients underwent HDC followed by autologous SCT in first remission. The experience with HDC followed by autologous SCT in the relapsed setting is rather limited, although there is some suggestion that persistent complete remission can be achieved in chemotherapy-sensitive disease.43 The use of allogeneic SCT in patients with PBL showed limited efficacy.54

Given the poor outcomes and survival of patients with PBL, novel agents are needed. The use of antimioma agents has been attempted on the basis of the plasmacytic differentiation of PBL cells, although the experience is limited to case reports. The proteasome inhibitor bortezomib has been shown to be effective in patients with post-GC DLBCL, inducing higher response and survival rates when used in combination with anthracycline-containing regimens.35 Bortezomib alone and in combination with chemotherapy has been used with limited efficacy in HIV-positive and HIV-negative patients with relapsed PBL.56-62 More recently, a case series of 3 previously untreated patients with PBL, 2 of them HIV-positive, has shown efficacy with the combination of bortezomib and dose-adjusted EPOCH.53 The immunomodulator lenalidomide induced a temporary response in a patient with relapsed PBL.56 Studies have shown that approximately 30% of PBL cases express the activation marker CD30,24,26,63 and a recent report showed response to brentuximab vedotin in a patient with CD30-expressing relapsed PBL.64 A specific cutoff for CD30 positive among lymphoma cells, however, has not been defined.

Our recommendation for first-line treatment of PBL is 6 cycles of infusional dose-adjusted EPOCH (with or without bortezomib) with intrathecal prophylaxis with each cycle of EPOCH and consideration of consolidative HDC followed by autologous SCT in first remission for appropriate candidates. In HIV-positive patients, cART should be started or optimized under the supervision of an infectious disease specialist with experience in the potential interactions between anticancer agents and cART. We recommend radiotherapy in the palliative setting, although it can be considered as consolidation in a case-by-case basis after a full course of combination chemotherapy has been administered.

Future directions

Potential therapeutic approaches for patients with PBL could include EBV-directed therapies in the form of antiviral agents or EBV-targeted cellular immunotherapy, and these approaches have not yet been evaluated in patients with PBL. Antiviral agents, such as ganciclovir, have been relatively unsuccessful because of the quiescent nature of the virus outside the lytic phase. Lytic viral activity results in elevation of thymidine kinase levels allowing antivirals to exert their effects through inhibition of viral DNA replication. Arginine butyrate has been shown to upregulate thymidine kinase activity and induce the lytic phase. A phase I/II trial of arginine butyrate with ganciclovir in 15 patients with refractory EBV-positive lymphoid malignancies showed limited activity with the exception of posttransplantation lymphoproliferative disorders, in which a response rate of 83% was observed.66 A study combining bortezomib and ganciclovir for EBV-associated lymphomas has recently been terminated for undisclosed reasons (NCT00093704). Cellular immunotherapy against EBV has been attempted in the form of EBV-specific cytotoxic T lymphocytes (CTLs) or chimeric antigen receptor (CAR) T cells. There are several limitations for the widespread use of CTLs, including lack of persistence and the long preparation time as well as the specialized facilities needed for their production.67 CAR T cells might be able to overcome some of the drawbacks of regular CTLs. An ongoing study is evaluating the therapeutic value of autologous EBV-specific CAR T cells with CD30 as the target (NCT01192464). Potentially, CAR T cells can be directed against EBV antigens in patients with EBV-associated lymphomas including PBL.

Another potential target of interest is the MYC gene. The MYC gene has been considered untargetable, given its lack of a binding domain.68 MYC heterodimerizes with the transcription factor Max, but the three-dimensional structure of this complex does not permit the positioning of small molecules.69 The transcriptional function of MYC can be targeted, however. MYC uses members of the bromodomain and extraterminal (BET) subfamily of bromodomain proteins such as BRD2, BRD3, and BRD4 to upregulate thymidine kinase activity and induce the lytic phase. A phase I/II trial of arginine butyrate with ganciclovir in 15 patients with refractory EBV-positive lymphoid malignancies showed limited activity with the exception of posttransplantation lymphoproliferative disorders, in which a response rate of 83% was observed.66 A study combining bortezomib and ganciclovir for EBV-associated lymphomas has recently been terminated for undisclosed reasons (NCT00093704). Cellular immunotherapy against EBV has been attempted in the form of EBV-specific cytotoxic T lymphocytes (CTLs) or chimeric antigen receptor (CAR) T cells. There are several limitations for the widespread use of CTLs, including lack of persistence and the long preparation time as well as the specialized facilities needed for their production.67 CAR T cells might be able to overcome some of the drawbacks of regular CTLs. An ongoing study is evaluating the therapeutic value of autologous EBV-specific CAR T cells with CD30 as the target (NCT01192464). Potentially, CAR T cells can be directed against EBV antigens in patients with EBV-associated lymphomas including PBL.

Conclusion

PBL remains a hard-to-diagnose and hard-to-treat lymphoma. Recent advances in the therapy of HIV-associated and aggressive lymphomas do not seem to have had a positive impact on the outcome of patients with PBL. Given the rarity and heterogeneity of PBL, it is likely that no large, randomized controlled therapeutic studies would ever be done.
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