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Plasmablastic lymphoma: better refine prognosis

Paul Coppo[1-3] and Laure Ricard[1,2] | [1]Assistance Publique–Hôpitaux de Paris; [2]Sorbonne Université; and [3]INSERM UMRS 1138

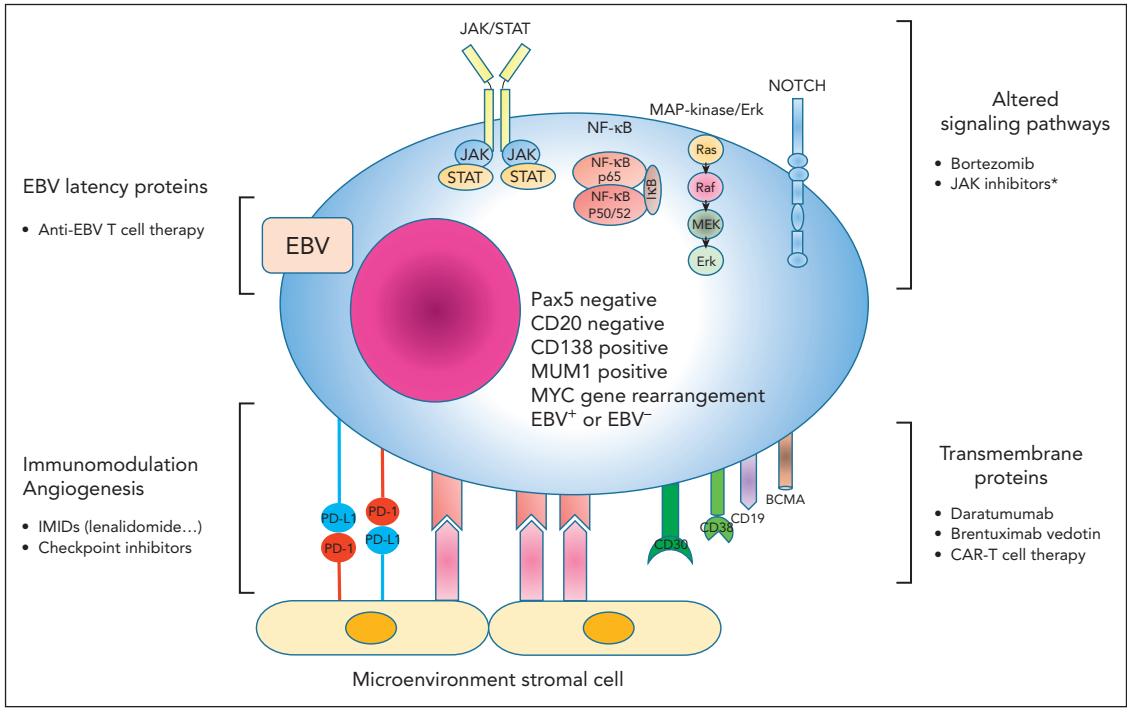
Plasmablastic lymphoma (PBL) is a rare and aggressive form of large B-cell lymphoma. There is no standard approach to treatment, and the prognosis of PBL has only been assessed through small case series. In this issue of *Blood*, Di Ciaccio et al[1] report a unique series of 281 patients, providing more definitive insights into the prognosis of PBL. The authors found that Epstein-Barr virus (EBV)-negative lymphoma, poor performance status, advanced stage, and bone marrow involvement were risk factors associated with inferior overall survival (OS). Prognosis remained dismal despite intensive regimens and the inclusion of proteasome inhibitors, bringing the authors to conclude that there is a need for new therapeutic strategies, especially for the highest-risk forms.

As first described in 1997, PBL most commonly arose in the oral cavity of patients with HIV.[2] It was recognized 11 years later by the World Health Organization classification as a rare and aggressive variant of large B-cell lymphoma occurring predominantly in males and accounting for 2% of AIDS-related lymphomas.[3] Subsequently, extraoral PBL was documented, with other common sites including the gastrointestinal tract and skin. It was also reported in other immunosuppressed states, including posttransplantation, systemic autoimmune disorders, and age-related immunosenescence.[4] Neoplastic cells resemble immunoblasts or plasmablasts and constitutively express the plasma cell antigen CD138 (syndecan-1). The tumor cells often have an immunoglobulin chain restriction with no or weak expression of B-cell mature markers, such as CD20, CD79a, and PAX5, and an increase in MYC rearrangement. PBL cells frequently express the EBV genome with type I latency (EBV^+ PBL), especially in patients with HIV, with a better 2-year event-free survival in EBV^+ PBL as compared with EBV^- PBL.[5] Whole exome sequencing and targeted deep sequencing of HIV^+ PBL showed alterations in JAK-STAT, MAPK-ERK, and NOTCH signaling pathways.[6] PBL evolves several patterns of immune escape involving the overexpression of immune checkpoints such as the programmed cell death protein-1 (PD-1) and its ligand (PD-L1) expressed on tumor cells or in their microenvironment, especially in tumor and microenvironment cells of EBV^+ PBL.[5] Hence, EBV infection induces an antiviral cytotoxic immunity, which progressively exhausts T lymphocytes and promotes the tolerogenic microenvironment of PBL. Despite recent advances in lymphoma therapeutic strategies, PBL is still considered an aggressive lymphoma with adverse prognosis.[7,8] Due to the rarity of this disease, most therapeutic data derive from pooled case reports, limiting the progress in the management of the disease. From available literature, cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone (CHOP) may not be adequate treatment, and more intensive regimens, typically EPOCH (etoposide, prednisolone, vincristine, cyclophosphamide, hydroxydaunorubicin), are generally preferred. The proteasome inhibitor bortezomib is known to inhibit nuclear factor-κ B (NF-κB) and works synergistically with hydroxydaunorubicin in primary effusion lymphomas. Since the plasmacytic differentiation is mediated by the antiapoptotic effects of NF-κB, regimens combining bortezomib and EPOCH have been explored and show promising results in case series of PBL with long-term survival.[9,10]

In the current study, Di Ciaccio and colleagues analyzed in an unprecedent international effort that involved 22 institutions across 4 countries, with 281 patients with PBL, to provide more insights on clinical presentation and prognosis of this form of lymphoma. They confirm that PBL typically occurs in the context of immune deficiency, identified here in 51% of cases, which included 35% with HIV. Prognosis was poor, with a median OS of 2.76 years (95% confidence interval [CI], 1.7-4.25) and an estimated 5-year OS of 36% (95% CI, 30%-42%). EBV^- lymphoma, poor performance status, advanced stage, and bone marrow involvement were associated with a worse OS. The International Prognostic Index was also predictive of outcomes, confirming previous findings.[5,7] The presence of an underlying immunosuppression, including HIV status, did not impact prognosis, although patients with immunodeficiency were clearly more likely to have EBV^+ lymphoma. In patients treated with curative intent, overall response rate was 72%, but neither the intensity of the treatment regimen nor the inclusion of proteasome inhibitors clearly improved OS. Altogether, these results provide more definitive findings with regard to prognosis in PBL but leave open the optimal treatment for this form of lymphoma.

This study has the unavoidable limitations of a retrospective design. Besides missing data regarding histopathological findings, conclusions regarding the efficacy of treatment approaches must be interpreted with caution as baseline characteristics and treatment modalities show significant heterogeneity. The role of proteasome inhibitors is an especially crucial issue and will require more formal assessment, with consensual predefined regimens and accurate evaluation before more definitive conclusions can be reached.

Despite these limitations, the results represent a meaningful basis for a better stratification of patients with PBL at a time when emerging therapies based on pathophysiological findings open



PBL cell: potential targeted therapies. BCMA, B-cell maturation antigen; brentuximab vedotin, anti-CD30 antibody-drug (monomethyl auristatin) conjugate; CAR-T, chimeric antigen receptor T-cell therapy; daratumumab, human IgG1 monoclonal antibody targeting the plasma cell marker CD38; IMIDs, immunomodulators including lenalidomide, thalidomide, pomalidomide. *Not yet evaluated.

promising avenues for improvement of PBL treatment. These include daratumumab, a human immunoglobulin G1 (IgG1) monoclonal antibody targeting the plasma cell marker CD38 and inducing cell death of $CD38^+$ cells by antibody-dependent cell cytotoxicity, and brentuximab vedotin, an antibody-drug (monomethyl auristatin) conjugate targeting CD30. The expression of PD-1 and PD-L1 on both PBL cells and microenvironment makes an attractive target for checkpoint inhibitors, especially in relapse and refractory cases. Other immunomodulatory drugs such as lenalidomide have established a pivotal role in myeloma treatment, so they have been used in patients with PBL with reasonable outcomes. Lastly, cell therapy strategies aimed at targeting EBV, as well as CD19 antigen or B-cell maturation antigen with chimeric antigen receptor T-cell therapy are also in process. In the light of these new potential therapeutic agents needing evaluation (see figure; reviewed in Kaur and Kollimuttathuillam[6]), the study presented by Di Ciaccio et al should provide a tool to better tailor forthcoming clinical trials in PBL. It also shows that large-scale collaboration is feasible in this rare form of lymphoma, which should encourage the development of international therapeutic programs.

Conflict-of-interest disclosure: The authors declare no competing financial interests. ■

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