EBV and memory B cells: an affair with consequences

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Hematopoietic stem cell transplant (HSCT) or solid organ transplant (SOT) recipients are often at high risk of developing Epstein-Barr virus (EBV)-associated lymphoproliferative disease (PTLD) due to underlying severe immunodeficiency. In particular, impairment of antiviral T-cell immunity as a result of immunosuppressive therapy is a critical risk factor for the development of PTLD. The impact of interaction between EBV with host B-cell subpopulations on the emergence of PTLD in transplant recipients has been a major area of interest for immunobiology experts. Understanding of these interactions may provide clues on how to control EBV-associated PTLD in transplant recipients. Early studies conducted by David Thorley-Lawson and colleagues first demonstrated that EBV persists in resting memory B cells in a nonpathogenic state with limited viral gene expression, which allows these cells to escape from antiviral T-cell control. Occasionally, these virus-infected memory B cells differentiate into plasma cells resulting in the activation of the EBV replicative cycle, which allows infection of more naive B cells. In this issue of Blood, Burns et al have now extended these observations to provide an interesting insight into the biology of EBV infection in HSCT recipients, especially in the context of reconstitution of innate and adaptive immune cells.

By prospectively monitoring EBV DNA in HSCT recipients, the authors of this study were able to identify patients who had high viral reactivation and others who had undetectable or low viral load. Follow-up analysis of these 2 groups of recipients revealed early emergence of CD27 memory B cells in patients with high viral loads and selective infection of these cells with EBV. These CD27 memory B cells express multiple latent transcripts including EBNA1, EBNA2, and LMP2 or LMP1 and also expressed the proliferation marker Ki-67.

These observations raise an important question on how the pathway of EBV infection in HSCT recipients may be different from healthy virus carriers. As shown in the figure, EBV infection in immunocompetent individuals proceeds through the infection of naive B cells, which is followed by migration to the germinal center where these cells differentiate into memory cells. Burns et al argue that this differentiation program is unlikely to operate in HSCT recipients as their normal germinal center activity is impaired due to the underlying deficiency of CD4 T cells and other supporting cells. They propose that in the HSCT setting, either EBV infects donor mature memory B cells (transferred with engrafted cells) or newly emerging mature B cells that have recently differentiated from donor stem cells. In this latter scenario, it is unclear whether EBV infects naive B cells and then drives them to differentiate into memory or directly infects rare memory B cells.

Alternative routes of EBV infection of B cells in immunocompetent and immunocompromised individuals. In healthy individuals, EBV-infected naive B cells are driven to differentiate into memory cells within the germinal center. By contrast, HSCT recipients have poor germinal center responses for several months after transplant. Therefore, it is proposed that EBV either infects memory B cells present in the graft or newly emerging mature B cells that have recently differentiated from donor stem cells. In this latter scenario, it is unclear whether EBV infects naive B cells and then drives them to differentiate into memory or directly infects rare memory B cells.
high viral load may prevent progression to PTLD.

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CLINICAL TRIALS AND OBSERVATIONS

Comment on O’Brien et al, page 2686

Idelalisib has CLL on the run!

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In this issue of Blood, O’Brien et al report mature results of initial treatment of chronic lymphocytic leukemia (CLL) with the PI3Kδ inhibitor idelalisib plus rituximab, and demonstrate that the combination is extremely effective with manageable toxicity in an older patient population. In the last several years, a revolution has occurred in the therapy of relapsed CLL. The approvals by the Food and Drug Administration of the Bruton’s tyrosine kinase inhibitor ibrutinib for relapsed CLL patients and those with 17p deletion, as well as the approval of idelalisib with rituximab for relapsed CLL patients in whom rituximab is appropriate therapy, have led to the rapid adoption of these targeted therapies as the agents of choice for relapsed CLL. The effectiveness of these drugs, particularly in patients with high-risk cytogenetic abnormalities like 17p deletion, has naturally led to interest in their use for initial therapy, particularly in older patients in whom chemotherapy is less well-tolerated. Yet upfront data have been quite limited.

In this article, O’Brien et al present the first clinical trial of idelalisib with rituximab for the initial therapy of CLL in patients with a median age of 71 years, 42% of whom had advanced-stage disease. The overall response rate is 97%, with 19% being complete responders, none of whom have progressed to date. The progression-free survival (PFS) is an impressive 83% at 36 months, with only 4 events of disease progression, despite only 23 of 64 patients currently continuing on idelalisib (see figure). Among the highest-risk TP53-mutated patients (n = 9), the overall response rate is 100% and none have progressed, consistent with the known excellent activity of idelalisib in relapsed patients in this high-risk group. Although this was a phase 2 study, these results compare very favorably with the current standard of care for this patient population—obinutuzumab chlorambucil—which has a median PFS of 29.2 months in a phase 3 study, and are similar to the smaller phase 1b/2 study of ibrutinib, which showed a PFS of 96% at 30 months, with only 2 TP53-mutated patients. These results certainly justify registration trials of idelalisib in this upfront setting.

Toxicity was not in substantial, however, with adverse events being the primary reason for discontinuation, occurring in 42% of patients. Grade 3 or higher diarrhea/colitis was seen in 42% of patients, compared with 14% in a recent summary of toxicity in 8 relapsed studies of idelalisib and 6% in the phase 1 study in very heavily pretreated patients. Grade 3 or greater transaminitis was seen in 23% of patients, compared with 14% in the early-relapse studies and 2% in the phase 1 study. Two cases of (fatal) pneumonitis and 2 cases of (reversible) pulmonary fibrosis were also observed.

This unique pattern of toxicity with idelalisib, namely colitis, hepatitis, and pneumonitis, is consistent across studies and is seen here to be paradoxically higher in untreated patients. This paradox could be resolved by an immunologic mechanism that might be more intact in less heavily treated patients. In this trial, these toxicities were primarily managed by holding drug, which is essential; but in addition, it has become increasingly clear that corticosteroids are a very effective treatment. Two recent studies characterizing the pathology of idelalisib-induced colitis have found CD8 T-cell infiltrates associated with crypt apoptosis as a common feature. Interestingly, the target of idelalisib, namely the δ isoform of the PI3K p110 catalytic subunit, is known to be critical for the survival and function of regulatory T cells, and genetic mutations that disrupt regulatory T-cell function in mice and humans lead to a very similar autoimmune syndrome of hepatitis, enteritis, and pneumonitis. In a mouse model of inflammatory bowel disease, adoptive transfer of wild-type T-regulatory cells, but not regulatory T cells deficient in PI3Kδ, abolishes autoimmune colitis. Taken together, these findings suggest that idelalisib toxicities may be a result of on-target inhibition of p110δ in regulatory T cells. Correlative studies in ongoing clinical trials will be needed to test this hypothesis in patients. Meanwhile, a high index of suspicion for autoimmune toxicity in patients on idelalisib, with early drug hold and consideration of corticosteroids once infection is ruled out or treated,
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