Antibody therapies show promise in the treatment of mature T and natural killer (NK) cell cancers. However, T-cell-directed antibody therapies have repeatedly been associated with Epstein-Barr virus-associated lymphoproliferative disease (EBV LPD). As reported in this issue of Clinical Cancer Research, splizumab, an anti-CD2 monoclonal antibody, was associated with EBV LPD in patients with lymphoma in a Phase I trial (1). O’Mahony and colleagues raise the question as to whether rituximab, a B-cell-depleting antibody, should be part of the platform for studying splizumab and similar antibodies in the future.

Why might rituximab therapy impact EBV LPD associated with splizumab? EBV is harbored mainly in resting B lymphocytes (Fig. 1A). Most of the genome is transcriptionally silent. Intermittent activation of the lytic cycle leads to production of new virions and infection of other B cells. Among these are cells that express the full panel of viral latency genes (unrestricted latency). These viral latency genes, in turn, drive proliferation of the cells and express immunodominant viral antigens. They are targeted by T cells and NK cells, and equilibrium is maintained.

When T cells are depleted, EBV LPD is often the result (Fig. 1B). First recognized in association with organ transplantation, EBV LPD is increased in patients treated with a monoclonal antibody selectively targeting T cells (2). Similarly, in allogeneic hematopoietic stem cell transplantation (HSCT), T cell depletion of the stem cell graft to prevent graft versus host disease (GVHD) increases the incidence of EBV LPD. Patients undergoing unmanipulated allogeneic HSCT have an ~1% risk of developing EBV LPD, whereas, at the other extreme, T cell depletion with antibodies specific for CD2 and CD3 was associated with EBV LPD in 71% of patients (3). A multivariate analysis in more than 18,000 allogeneic HSCT recipients identified T cell depletion as a risk factor for EBV LPD, but the risk associated with depletion varied with the particular method of depletion employed (4). The use of sheep red blood cell rosetting, anti-T, or anti-T and -NK antibodies was associated with relative risks of greater than 10-fold, whereas methods that resulted in a balanced loss of B cells and T cells were not associated with increased risk. The use of anti-CD3 antibody to treat GVHD is an even greater risk factor for EBV LPD than selective T cell depletion to prevent GVHD (4). It seems likely that the protective effects of B cell depletion reflects both decreased numbers of virus carrying donor lymphocytes and the elimination of the target cell for transformation (Fig. 1C). In patients with congenital selective absence of B cells (X-linked agammaglobulinemia), there is no known EBV-associated disease and an EBV carrier state appears not to be established (5). Thus, O’Mahony and colleagues proposed to study splizumab in the context of B cell depletion such as might be achieved with rituximab.

Rituximab is regarded by many as the first line treatment for EBV LPD (6). The complete response rate in solid organ transplant recipients was 44% in a multicenter trial (6). It has also been used to treat high-risk transplant recipients (“preemptive therapy”) (refs. 7, 8). Discussion of a “rituximab platform” for the study of T-cell-depleting antibodies raises concerns that rituximab may contribute to general immune dysfunction. In particular, attention has focused on progressive multifocal leukoencephalopathy, bacterial infection, and reactivation of hepatitis B and C viruses. Progressive multifocal leukoencephalopathy is a devastating outcome, but it remains exceedingly rare even in rituximab-treated patients. Given the lethality of the tumors being treated, the possible risk is likely justified. Hepatitis virus reactivation is a concern, although the magnitude of increased risk is difficult to estimate. It might be appropriate to exclude such patients from trials involving a rituximab platform.

In summary, the risk of EBV LPD may not be a reason to abandon further investigation of T- and NK-cell-depleting antibody therapies for treatment of peripheral T cell malignancies. Rather, as suggested by O’Mahony and colleagues, there is good justification for cautious further exploration in
the context of a therapeutic platform that includes B cell depletion.

References


Evaluation of T- and NK-Cell-Targeted Therapies: Is There a Role for Rituximab Prophylaxis?

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