

XIII. The role of immunotherapy in the treatment of lymphoma

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Passive immunotherapy with monoclonal antibodies has transformed the treatment of lymphoma. The first demonstration of efficacy of antibodies was with a customized product directed against the unique idiotype expressed by each patient's tumor. Although effective, this proved impractical. Rituximab, the chimeric antibody directed against CD20, a target expressed by all mature B cells, proved safe and effective and was the first US Food and Drug Administration (FDA)-approved antibody for the treatment of malignancy. This antibody has found widespread use both as monotherapy and when combined with chemotherapy. It is now used for initial therapy and in the treatment of recurrent disease and in maintenance of remission. Second-generation monoclonal antibodies targeting CD20, with improved killing activity, are now in clinical trial and one has recently received FDA approval for the treatment of chronic lymphocytic leukemia (CLL). Improving the killing activity of antibodies has worked by coupling them to radioisotopes or to cytotoxic molecules. This has been especially successful with an antibody against CD30 for Hodgkin lymphoma and one against CD22 for hairy cell leukemia. Antibodies against other targets on B and T cell lymphomas are also being tested, including CD19, CD52, CD40, CD80 and CD79. Antibodies against targets on the host immune system, including CTLA4, PD-1, CD137 are being tested in the hope of augmenting the effectiveness of another tumor-targeted antibody or facilitating an immune response against the tumor. One intriguing approach is

a bispecific antibody containing binding sites for both CD19 and CD3, bridging the tumor cell to T cells. Finally various passive cellular therapies are being tested, including allogeneic T cells, autologous T cells engineered to express chimeric T-cell receptors against B-cell targets or engrafted T-cell receptors recognizing peptides processed and presented on the surface of the tumor.

Active immunotherapy would have the advantage of immunologic memory and recognition of multiple independent targets on the tumor cell. However, in order for this to work immunosuppressive effects of the tumor, such as cytokines, T regulatory cells and myeloid suppressor cells, must be overcome. Three separate phase III trials of vaccination against the custom idiotype of each lymphoma patient's tumor have failed to demonstrate improved progression-free survival (PFS), despite promising phase II trials, although there may be interesting hypotheses yet to emerge as various subsets of these data are examined and reported. Other, more broadly focused vaccine approaches, including whole tumor cells fused to dendritic cells or intratumoral injections of immunostimulatory agents have shown promising results of tumor regressions. In the future, combinations of active and passive immunotherapy approaches are likely to yield even better effects. Particularly appealing would be combinations of small molecules targeted against critical signaling pathways with passive and active immunotherapies. Hopefully these less toxic immunotargeted therapies of the future will take the place of the cytotoxic therapies of the present.