Monoclonal Antibody Therapy in WM

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The development of monoclonal antibody (MAB) therapy and the introduction of the anti-CD20 MAB rituximab radically changed the treatment paradigm for patients with B cell malignancies and has been widely incorporated into all standard front-line and most relapsed settings in the treatment of patients with indolent and aggressive non-Hodgkin's lymphomas (NHL's). This has resulted in improved progression free (PFS) and overall (OS) survivals in patients with indolent NHL (follicular), aggressive (diffuse-large B cell) and chronic lymphocytic leukemia (CLL). In the indolent histologies, maintenance R is increasingly common and associated with improved PFS compared with observation. WM is a B cell malignancy, often with a initial indolent course that is characterized by the expression of antigens that have been targeted with MAB including CD20, CD19, CD22 and CD52. Rituximab therapy has been a mainstay of therapy of WM as a single agent and in combination with conventional or other targeted agents.

MAB therapy kills tumor cells using several potential mechanisms of action. The most important of these include 1) interaction with host FC receptor bearing cells including monocytes, macrophages and NK cells leading to antibody-dependent-cell mediated-cytotoxicy (ADCC); 2) activation and fixation of complement proteins leading to cell lysis or opsinization; 3) direct antiproliferative activity of the MAB binding to the cell surface protein (growth inhibition or apoptosis); 4) targeting of a drug, toxin or radionuclide, or; 5) interaction (synergy) with other targeted or conventional chemotherapies. The contribution of each of these mechanisms actually observed in the clinic is partly due to properties of the antigen targeted, the antibody and characteristics of the tumor cell. Despite nearly 15 years of clinical use, the most dominant mechanisms of action of R are still widely debated, although ADCC and complement fixation seem the most relevant.

Building on the success of Rituximab, several next generation anti-CD20 MAB's with augmented mechanisms of action are being evaluated. Ofatumumab is a human antibody with greater complement activity than rituximab in *in vitro* assays against tumor cells with low CD20 density. It is approved in the US for patients with refractory CLL, but is now being evaluated in other histologies. GA-101 is a new type 2 anti-CD20 antibody with greater direct anti-proliferative effects *in vitro* than rituximab, that is being evaluated in head-to-head comparison to rituximab.

In WM, the bulk of the existing clinical data is with R as single agent induction, use of R-chemo containing regimens and increasingly as a maintenance therapy following response to induction treatment. Unfortunately there is limited phase III trial data to guide usage. R is B cell specific with limited off target effects with the major toxicity being infusion related symptoms and some degree of immunodeficiency- generally due to hypogammaglobulinemia. In contrast, the anti-CD52 antibody, alemtuzumab, is associated with significant clinical activity, but limited by more severe immunosuppression due to CD52 expression on both B and T cells. Newer approaches including drug and toxin conjugated antibodies are being explored.