Rituximab-based treatments in Waldenstrom's macroglobulinemia

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Rituximab is a chimeric human/mouse antibody that targets the CD20 antigen which is almost always present on the surface of Waldenström's macroglobulinemia (WM) cells. Rituximab as monotherapy, using a standard 4 weekly infusions schedule, induces at least 50% reduction of serum monoclonal protein in 35% of untreated and in 20% of pretreated WM patients. These figures are higher when an extended rituximab dose regimen (repeat of 4 weekly infusions) is used. Response after single-agent rituximab is slow and a transient increase in serum IgM levels (IgM flare) is common but this does not indicate treatment failure.

Because rituximab is non-myelosuppressive, it can be combined with chemotherapy. Combinations of rituximab with nucleoside analogues (cladribine or fludarabine) with or without cyclophosphamide are associated with high response rates in both previously untreated and in previously treated patients. However, nucleoside analogues are immunosuppressive and stem cell toxic and recent reports indicate a small risk of disease transformation and of myelodysplastic syndromes. Thus, limited exposure to such regimens is advised, especially in younger WM patients. These regimens are particularly useful for rapid control of the disease, as in patients with symptomatic hyperviscosity, or severe cryoglobulinemia.

Combinations of rituximab with chemotherapy not containing nucleoside analogues, such as the DRC regimen (dexamethasone, rituximab and cyclophosphamide) or rituximab-CHOP are very effective, rapidly active and non-stem cell toxic. These regimens are widely used in the every day practice and are particularly suitable when collection of stem cell is considered.

In vitro experiments suggested that the immunomodulatory drugs thalidomide and lenalidomide enhance rituximab's activity. Thalidomide combined with rituximab is very active but due to peripheral neuropathy a dose reduction of thalidomide may often be required. Lenalidomide was also combined with rituximab, but hematologic toxicity was significant. Recent studies indicate that rituximab can be combined with the proteasome inhibitor bortezomib. The activity of this combination in previously untreated patients is very high. However, neurotoxicity can be a problem. Thus, ongoing studies assess a weekly administration of bortezomib which may be less neurotoxic.

Today rituximab-based combinations represent the most commonly used primary treatment for WM. Depending on the specific clinical setting different rituximab-based combinations can be used. Most patients receive rituximab combined with chemotherapy while the role of rituximab maintenance therapy in WM patients has to be determined. For some selected patients with low risk disease single agent rituximab may be appropriate while may also be used for the treatment of IgM-related neuropathies and is an active treatment for cold-agglutinin anemia.