Should maintenance rituximab be used for patients with Waldenstrom macroglobulinemia? [NO]

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Rituximab has become part of first-line treatment in most patients with Waldenströms macroglobulinemia as prospective trials have shown benefits in response and progression-free survival (PFS) compared to chemotherapy alone. Also rituximab single therapy leads to good responses with minimal toxicity. Rituximab used as single-agent as induction therapy is mostly scheduled for 4 weeks (375 mg/m^2 once per week). An extended therapy with 4 more weekly infusions has shown superior results. The use of rituximab as maintenance is less well studied in WM.

In follicular lymphoma (FL), 4 weeks induction with single rituximab followed by maintenance has been successful. In one trial with long-term follow-up, 45% of previously untreated patients responding to the induction and randomized to prolonged exposure to rituximab (one infusion every 2 months x 4), were still event-free at 8 years. Patients with previously untreated FL responding to immunochemotherapy (R-CHOP, R-CVP) have a superior PFS and a longer time to next antilymphoma treatment with rituximab maintenance. Also relapsed/resistant previously rituximab naïve FL patients responding to CHOP or R-CHOP show a benefit from rituximab maintenance.

The good results of rituximab maintenance in FL may not be applicable to WM patients, although one observational study has suggested improved clinical outcomes in responders to induction with a rituximab-containing regimen.

Both in FL and WM the optimum dose and schedule of rituximab is unknown in induction as well as in maintenance. The response to rituximab might be different in WM, which will be one of the issues for the debate.

With extended schedules of rituximab, B-cell depletion is prolonged and also serum immunoglobulin deficiencies are seen. In WM, the lowering of monoclonal serum IgM is a marker of response, but the level of serum concentrations of normal IgM and IgG has also been shown to fall. In some WM patients a "flare" of IgM has been described. With rituximab maintenance there is an increased rate of infections, mostly non-severe bronchitis and sinusitis.

New knowledge about the interaction between WM tumor cells and the bone marrow microenvironment, as well as deregulation in signaling pathways, has evoked interest in novel therapeutic agents. The combination of the proteasome inhibitor, bortezomib, and rituximab has exhibited significant activity with minimal neurological toxicity, especially if bortezomib is administered weekly. Other clinical trials include inhibitors to protein kinase C, histone deacetylase, phosphatidylinositol 3-kinase and mTOR (temsirolimus and everolimus). Also drugs affecting the signalling from the B-cell receptor (BCR) such as inhibitors to Bruton's tyrosine kinase (BTK), as well as new monoclonal antibodies are under way. When compared with chemotherapeutic agents and rituximab maintenance, some of these agents may be more effective and lead to better quality of life for patients with WM.

Summary: In WM, there is still no clear evidence for supporting the use of rituximab maintenance and prospective randomized studies are needed.