Clinical characteristics of Rituximab intolerance in patients with Waldenström's Macroglobulinemia.

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Introduction: Rituximab is a chimeric anti-CD20 monoclonal antibody used for the treatment of both untreated and previously treated patients with Waldenström's Macroglobulinemia. Rituximab is often associated with infusion-related reactions (IRR) during the first infusion which is associated with a well described cytokine release syndrome. Rituximab is also associated with depletion of uninvolved immunoglobulins leading to symptomatic hypogammaglobulinemia associated with recurring infections in many patients. In this study, we present data on patients who developed intolerance to rituximab defined as cessation of rituximab therapy outside of infusion related first-cycle IRRs, and symptomatic hypogammaglobulinemia.

Methods: We performed a retrospective chart review within the clinical database of our center for patients with the consensus clinicopathological diagnosis of WM between 1996 and 2013, and for whom rituximab therapy was prematurely truncated. We excluded patients who experienced first-cycle IRRs and patients in whom rituximab was stopped due to symptomatic hypogammaglobulinemia. Clinical and laboratory data were collected and tabulated, and are presented using descriptive statistics.

Results: We identified 40 WM patients who were considered intolerant to rituximab. The median age at WM diagnosis for these patients was 60.5 years (range 35-83 years). There was a male predominance of 2:1. The median number of therapies prior to becoming rituximab intolerant was 1 (range 0-5 lines). Fifty percent of patients were not previously exposed to rituximab. Fifty-three percent of patients became rituximab intolerant while receiving single agent rituximab, 18% while receiving bortezomib-based therapy, 15% while receiving cyclophosphamide-based therapy and 8% while receiving bendamustine-based therapy. Forty percent of patients developed rituximab intolerance while undergoing induction therapy, and the remaining 60% became intolerant during maintenance phase. The most common reasons for stopping rituximab were fever, chills, facial swelling, shortness of breath, hypotension, back pain, hives, chest pain, and serum sickness-like symptoms. The median serum IgM prior to development of rituximab intolerance was 3,053 mg/dl (range 550-9000 mg/dl), the median hemoglobin was 10.4 g/dl (8.2-14.5 g/dl), the median platelet count was 300 x 10^9/L (range 93-913 x 10^9/L), and the median bone marrow involvement was 35% (range 5-90%). Twenty-one percent of patients had familial WM, and 65% of patients were responding at the time of intolerance. Importantly, 20% percent (n=8) of patients received ofatumumab after developing rituximab intolerance, of whom 7 (87%) subsequently tolerated ofatumumab without incidence.

Conclusions: We present data on 40 WM patients who became intolerant to rituximab outside of the context of first-cycle IRRs, and symptomatic hypogammaglobulinemia. Our study shows that rituximab can be associated with a variety of symptoms that prompt cessation of therapy, and that most patients show a response to therapy despite intolerance. The use of ofatumumab is feasible and well tolerated in patients intolerant to rituximab. Additional research is needed to better understand the pathophysiology behind rituximab intolerance in this patient population.