

Rituximab intolerance in patients with Waldenström macroglobulinaemia

Rituximab is an anti-CD20 monoclonal antibody associated with improved response and overall survival (OS) rates in patients with B-cell lymphoproliferative disorders. Waldenström macroglobulinaemia (WM) is characterized by the malignant accumulation of IgM-producing lymphoplasmacytic cells in the bone marrow. WM cells brightly express CD20 and rituximab is one of the most commonly used agents to treat WM worldwide. We have observed, however, that a proportion of patients with WM exposed to single-agent rituximab or rituximab-containing regimens had to discontinue rituximab due to worsening infusion-related reactions (IRRs) as treatment with rituximab continued. This study aimed to investigate the incidence of 'rituximab intolerance' and to describe the characteristics of WM patients who become rituximab intolerant.

We searched our database for patients with a clinicopathological diagnosis of WM (Owen *et al*, 2003) between 2000 and 2014. From a total of 1466 patients with WM seen at our centre, 283 patients (19%) were excluded because they were not exposed to rituximab. From the remaining 1183 patients, rituximab therapy was discontinued in 130 patients (11%). We then excluded 45 patients in whom rituximab was discontinued in the setting of first infusions, severe neutropenia, recurrent or severe infections or symptomatic hypogammaglobulinaemia. Finally, 85 patients (7%) were deemed intolerant to rituximab and were included in this analysis.

The median age at WM diagnosis was 59 years (range 31–85 years). The median age at rituximab intolerance was 63 years (range 40–86 years), and the median time from WM diagnosis to rituximab intolerance was 3 years (range 0–19 years; Fig 1A). The male:female ratio was 1.4:1. The age and sex distribution of rituximab-intolerant WM patients was not different to our entire WM cohort (data not shown). The median number of therapies prior to rituximab intolerance was 1 (range 0–7). Twenty-nine patients (34%) developed rituximab intolerance during the first line of treatment, and 13 (15%) during the first year of rituximab exposure. At the time of rituximab intolerance, 41 patients (48%) were receiving single-agent rituximab, 24 (28%) alkylating agent-based therapy, 13 (15%) proteasome inhibitor-based therapy and 5 (6%) nucleoside analog-based therapy. Fifty-six patients (66%) had been exposed to rituximab in previous lines of treatment. The median time from first rituximab exposure to intolerance was 1 year (range 0–12 years; Fig 1B). A list of the most common symptoms leading toward rituximab discontinuation is shown in Table I. The median IgM prior to rituximab intolerance was 27.92 g/l (range 5.49–9.47 g/l) and the median haemoglobin concentration was 106 g/l (59–145 g/l). Eight patients (11%) presented in the context of IgM flare, and 49 (64%) were responding to rituximab at the time of intolerance. After rituximab discontinuation, 22 patients (29%) were exposed

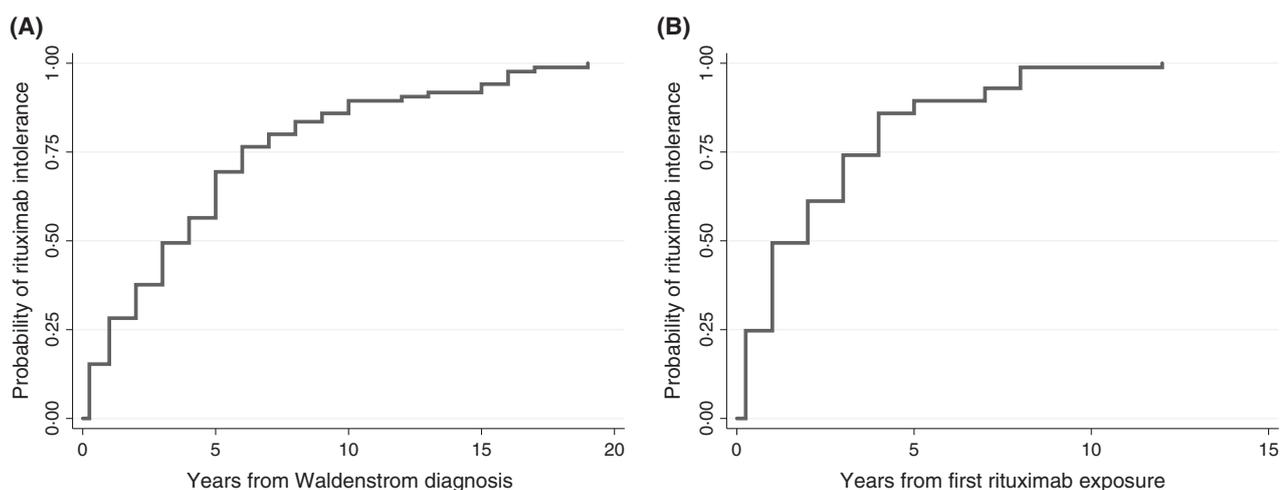


Fig 1. Time from diagnosis of Waldenström macroglobulinaemia to rituximab intolerance (A), and time from first rituximab exposure to rituximab intolerance (B).

Table I. Symptoms that prompted discontinuation of rituximab in rituximab-intolerant WM patients with Waldenström macroglobulinaemia.

Symptoms	N (%)
Anaphylaxis	20 (24)
Chills and rigors	15 (18)
Hives	13 (15)
Hypotension	13 (15)
Shortness of breath	11 (13)
Pruritus without rash	8 (9)
Rash except hives	8 (9)
Angioedema	7 (8)
Chest pain	7 (8)
Nausea and vomiting	6 (7)
Fever	5 (6)
Serum sickness	4 (5)
Syncope	3 (4)
Back pain	2 (2)
Cardiac arrhythmia	2 (2)
Stroke-like symptoms	1 (1)
Diarrhoea	1 (1)
Not otherwise specified	2 (2)

to the anti-CD20 monoclonal antibody ofatumumab; 18 (82%) of these patients tolerated and responded to this drug.

Several prospective studies have shown that rituximab alone or in combination is an effective agent in patients with WM, giving a strong rationale to treat appropriate WM patients with rituximab in the upfront and relapsed settings (Treon *et al*, 2005; Buske *et al*, 2009; Rummel *et al*, 2013). One of the most common adverse events associated with rituximab are IRRs. The likelihood of IRRs is higher during the first infusion but decreases with subsequent infusions. In contrast, we identified approximately 7% of WM patients in whom IRRs intensified with each infusion, to the point that rituximab had to be discontinued. Half of the patients were rituximab-naïve. Patients became intolerant while receiving rituximab as single agent or in combination, or while undergoing induction or maintenance therapy. Rituximab intolerance was seen at any level of serum IgM. Approximately 30% of rituximab-intolerant patients went on to receive ofatumumab, which was tolerated and produced a response in 80% of these cases.

The rate of rituximab discontinuation due to intolerance might be higher in patients with WM than in patients with other B-cell disorders. In the PRIMA study, which included over 1000 patients with follicular lymphoma (FL), one patient (0.2%) had to discontinue therapy due to hypersensitivity to rituximab (Salles *et al*, 2011). Another study of approximately 300 patients with FL randomized to chemotherapy with and without rituximab reported a 1.2% rate of rituximab discontinuation (Marcus *et al*, 2005). Similarly, in a randomized study comparing the addition of rituximab to fludarabine and cyclophosphamide in patients with

chronic lymphocytic leukaemia, one episode (0.25%) of cytokine release syndrome was reported in over 400 patients exposed to rituximab (Hallek *et al*, 2010). Other large studies, such as RESORT, STIL and REACH, did not report rates of rituximab discontinuation.

We also performed a review of prospective trials using rituximab in WM patients. Rituximab discontinuation was not specifically reported in the majority of the studies and most of the studies might have been too small to show the outcome of interest. However, in a study using cladribine and rituximab (Laszlo *et al*, 2010), two patients (6.9%) experienced IRRs that led to rituximab discontinuation. In a study using lenalidomide and rituximab (Treon *et al*, 2009a), one patient (6.3%) discontinued rituximab due to anaphylaxis. In a study combining fludarabine and rituximab (Treon *et al*, 2009b), three patients (6.9%) discontinued rituximab due to severe IRRs.

We acknowledge that this is a retrospective study and is prone to selection bias. The patients seen at our centre might have specific features that make them more prone to develop rituximab intolerance, or our cohort might not be representative of patients in other centres or in the community. However, the decision of discontinuing rituximab was not made by us in all cases, which means that other physicians in other centres also felt there was the need to stop rituximab based on patients' symptoms.

In summary, we would like to bring to the clinicians' attention the occurrence of rituximab intolerance, which seems to affect a higher proportion of patients with WM than with other B-cell malignancies. Rituximab is a highly effective treatment for patients with WM, and rituximab intolerance should not deter practitioners from its use. Further research is needed to confirm our findings, and also to clarify the mechanisms behind this phenomenon.

Authorship

JJC, ZRH and SPT designed the study, and analysed the data. JJC, SK, KM and RM gathered the data. JJC wrote the initial draft. All authors reviewed and approved the final manuscript.

Disclosures

The authors have no conflicts of interest to disclose.

Jorge J. Castillo^{1,2}

Sandra Kanan¹

Kirsten Meid¹

Robert Manning¹

Zachary R. Hunter¹

Steven P. Treon^{1,2}

¹Bing Center for Waldenström Macroglobulinemia, Dana-Farber Cancer Institute, and ²Harvard Medical School, Boston, MA, USA.

E-mail: jorgej_castillo@dfci.harvard.edu

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