Higher risk of rituximab intolerance in patients with Waldenström Macroglobulinemia

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Introduction

Rituximab is a chimeric anti-CD20 monoclonal antibody commonly used alone or in combination for the treatment of patients with Waldenström Macroglobulinemia (WM).

Rituximab is an efficacious therapy for WM but has been associated with infusion-related reactions (IRR), especially during the first infusion.

In this study, we present data on patients who developed intolerance to rituximab defined as the need of stopping rituximab therapy outside of the context of first-cycle IRRs, recurrent infections or severe hypogammaglobulinemia.

Methods

We performed a retrospective chart review within the database of our institution looking for cases with a clinicopathological diagnosis of WM between 1996 and 2014 (n=1,466 records).

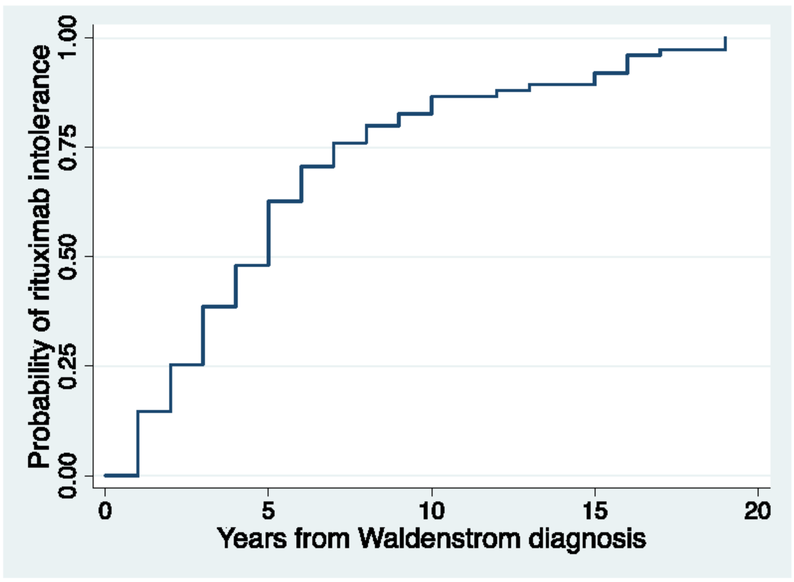
Key inclusion criteria were patients >18 years with a clinicopathological diagnosis of WM, who were either untreated or previously treated in whom rituximab therapy had to be stopped.

We excluded patients who were not exposed to rituximab (n=283), and patients who experienced first-cycle IRRs and patients in whom rituximab was stopped due to severe hypogammaglobulinemia or the onset of recurrent or life-threatening infections (n=45).

Eighty-five patients (7.1% of our cohort) met the above criteria. Clinical and laboratory data were collected and tabulated, and are presented using descriptive statistics.

The median time from WM diagnosis to rituximab intolerance was estimated using the Kaplan-Meier method for incomplete observations.

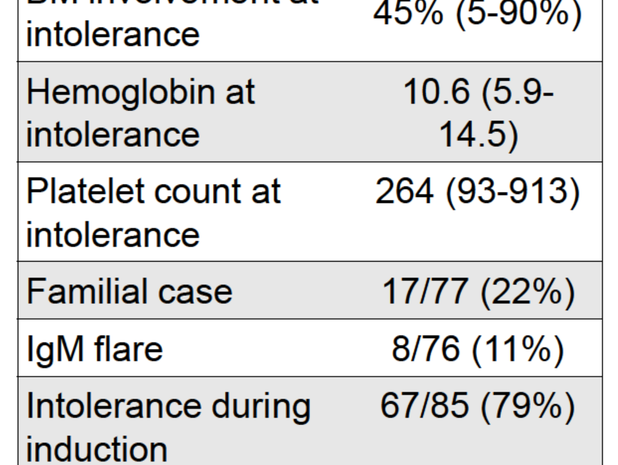
Results



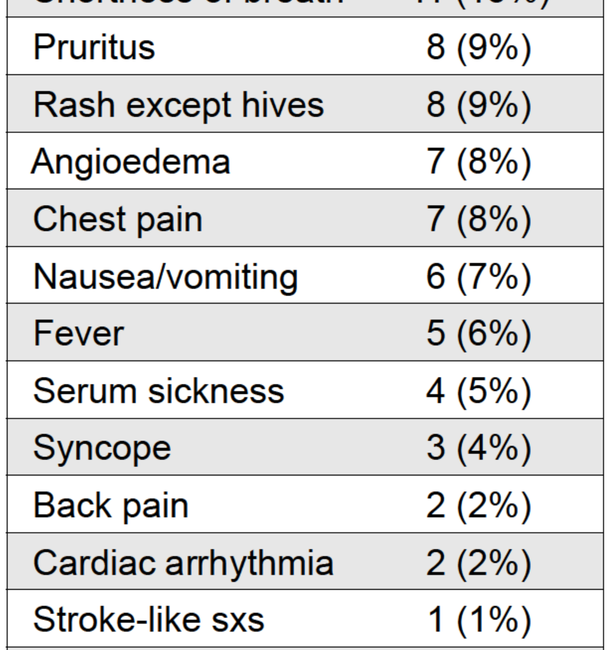
Kaplan-Meier estimate for time from WM diagnosis to rituximab intolerance

Patients characteristics	Number (%) Or median (range)
Age at WM diagnosis	59 (31-85)
Age at intolerance	63 (40-86)
Men	50/85 (59%)
Previous lines	1 (0-7)
IgM level at intolerance	2,792 (549-9,470)
BM involvement at intolerance	45% (5-90%)
Hemoglobin at intolerance	10.6 (5.9-14.5)
Platelet count at intolerance	264 (93-913)
Familial case	17/77 (22%)
IgM flare	8/76 (11%)
Intolerance during induction	67/85 (79%)
Intolerance during maintenance	18/85 (21%)
Response at intolerance	49/76 (64%)
Partial response	30/49 (61%)
Minor response	19/49 (39%)

Symptoms related to rituximab intolerance	
Anaphylaxis	20 (24%)
Chills and rigors	15 (18%)
Hives	13 (15%)
Hypotension	13 (15%)
Shortness of breath	11 (13%)
Pruritus	8 (9%)
Rash except hives	8 (9%)
Angioedema	7 (8%)
Chest pain	7 (8%)
Nausea/vomiting	6 (7%)
Fever	5 (6%)
Serum sickness	4 (5%)
Syncope	3 (4%)
Back pain	2 (2%)
Cardiac arrhythmia	2 (2%)
Stroke-like sxs	1 (1%)
Diarrhea	1 (1%)
Unspecified	2 (2%)



Regimens received by WM patients at intolerance



Subsequent exposure to ofatumumab, and intolerance to ofatumumab

Systematic review for rituximab discontinuation in other chronic lymphoproliferative disorders

- Marcus (2004)
  - Follicular lymphoma
  - R-CVP vs. CVP
  - 2/162: 1.2%
- PRIMA (2013)
  - Follicular lymphoma
  - Maintenance rituximab vs. observation
  - 1/500: 0.2%
- RESORT (2012)
  - Follicular lymphoma
  - Maintenance rituximab vs. re-treatment
  - Not reported
- CLL8 (2011)
  - Frontline CLL
  - FCR vs. FC
  - 1/400: 0.25%
- REACH (2011)
  - Relapsed CLL
  - FCR vs. FC
  - Not reported but same number of patients in both arms discontinued therapy
- STIL (2013)
  - Indolent NHL
  - Bendamustine-R vs. R-CHOP
  - Not reported

Conclusions

Rituximab intolerance leading to treatment cessation can be seen in approximately 7% of patients with WM, and can be prompted by a variety of symptoms.

The rate of rituximab intolerance leading to discontinuation in patients with WM appears higher than in patients with other B-cell lymphoproliferative disorders.

Most patients showed response to rituximab at the time of intolerance, and most of the times it was not associated with an IgM flare.

The use of ofatumumab is feasible and well tolerated in patients intolerant to rituximab.

Disclosures

The authors have no conflict of interest to disclose.

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Indolent lymphoma
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