Ixazomib, dexamethasone and rituximab (IDR) as primary therapy for symptomatic Waldenström macroglobulinemia

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Background

Waldenström macroglobulinemia (WM) is an incurable B-cell lymphoma characterized by the accumulation of IgM-secreting lymphoplasmacytic cells in the bone marrow and other organs.
Bortezomib in combination with rituximab and dexamethasone (BDR) is highly active as primary therapy in WM, though treatment-related neuropathy is common with BDR in WM, and often leads to premature treatment discontinuation (Treon J Clin Oncol 2009; Dimopoulos Blood 2013).
Ixazomib is a neuropathy-sparing, orally administered proteasome inhibitor that is active in myeloma, which has not been previously evaluated in WM.

Methods

Symptomatic, previously untreated patients with a clinicopathological diagnosis of WM, and meeting criteria for initiation of therapy, were included in this prospective, single-arm phase II study.
Treatment consisted of ixazomib 4 mg PO on days 1, 8 and 15 + dexamethasone 20 mg PO/IV on days 1, 8 and 15 + rituximab 375 mg/m2 IV on day 1 (IDR) for six 4-week cycles (induction) followed by six 8-week cycles (maintenance).
Rituximab was held for the first two cycles of therapy to minimize risk of IgM flare.
Zoster prophylaxis and proton pump inhibitors were administered throughout IDR therapy.
The study was approved by the institutional review board at the Dana-Farber Cancer Institute, and registered under Clinicaltrials.gov ID NCT02400437.

Results

Twenty patients have completed the induction phase of therapy at this time

Table 1. Baseline Characteristics of the patients

Characteristic	Patients (N=26)
Age at WM diagnosis – yr	63 (46-81)
Age of treatment initiation – yr	65 (46-82)
Hemoglobin – g/dL	10.2 (6.9-13.2)
Serum IgM – mg/dL	5,068 (653-7,650)
Bone marrow involvement - %	55 (5-95)
Lymphadenopathy – no. (%)	46 (12)
Splenomegaly	12 (3)
MYD88 L265P	100 (26)
CXCR4 WHIM	58 (15)
Nonsense	67 (10)
Frameshift	33 (5)
Criteria for treatment initiation – no. (%)	13 (48.1)
Anemia	1 (3.8)
Symptomatic splenomegaly	7 (27)
Hyperviscosity	4 (15.4)
Peripheral neuropathy	5 (19.2)
Constitutional symptoms	1 (3.8)
IgM >6,000 mg/dL	1 (3.8)
Pancytopenia	

Following induction therapy, the median serum IgM level decreased to 2,315 (range 287-5,820 mg/dL), median hemoglobin increased to 12.75 (range 10.4-14.6 g/dL), and median bone marrow involvement decreased to 17.5% (range 0-76%). P-value <0.001 for all comparisons against baseline.

Results

Figure 1. Depth of response based on CXCR4 mutational status

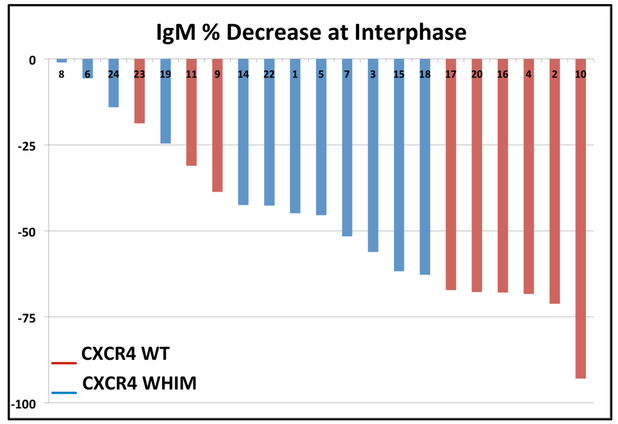
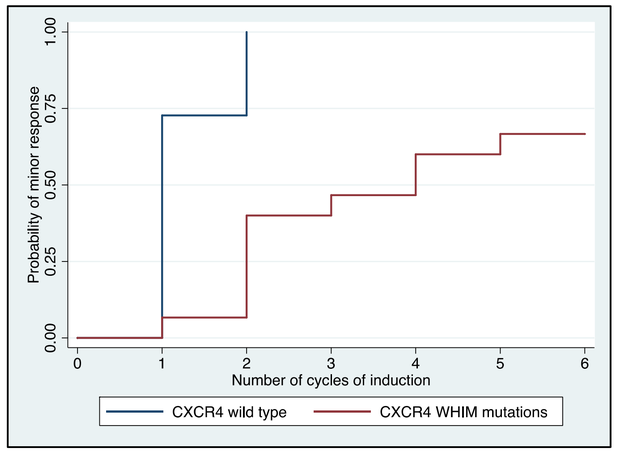


Figure 2. Time to response based on CXCR4 mutational status



Results

The median time to response was 8 weeks.
The median time to minor response in CXCR4 mutant patients was 4 cycles versus 1 cycle in wild-type CXCR4 patients (log rank p=0.0001).
Using consensus response criteria, the overall response rate was 80% (VGPR 5%, PR 45%, MR 30%) with a major response rate of 50%.
Major responses (VGPR + PR) at Interphase were observed in 40% of patients with CXCR4 mutations versus 55% in those who were wild-type CXCR4 (p=0.69).
Overall responses (MR or better) at Interphase were observed in 67% of patients with CXCR4 mutations versus 100% in those who were wild-type CXCR4 (p=0.05).
Five patients have been taken off study:

- 2 for lack of response
- 1 due to lack of clinical benefit with persistent failure to thrive while in PR
- 1 for progressive neuropathy while in PR although in part due to worsening of diabetic neuropathy
- 1 due to comorbidities prohibiting further treatment while in PR.

No other grade 3 or 4 adverse events were reported.

Conclusion

These preliminary data suggest that the combination of IDR is an active, well-tolerated, neuropathy-sparing regimen in symptomatic untreated WM patients.
CXCR4 mutational status might affect time to and depth of response to IDR.

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