Prospective Phase II Clinical Trial of Carfilzomib, Rituximab and Dexamethasone (CARD) in Patients with Symptomatic Waldenstrom's Macroglobulinemia (WM).

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Introduction

Carfilzomib is a novel proteasome inhibitor recently approved for the treatment of relapsed/refractory multiple myeloma, and associated with a low incidence of peripheral neuropathy in myeloma patients. Bortezomib, a proteasome inhibitor that is active in WM, is associated with significant peripheral neuropathy by standard administration with upwards to 30% of patients experiencing grade 3 peripheral neuropathy (Treon et al, JCO 2009). The activity of carfilzomib has not been formally examined in WM. We therefore conducted a prospective Phase II clinical trial of carfilzomib, rituximab and dexamethasone (CARD) in patients with symptomatic Waldenstrom's macroglobulinemia (WM) who were proteasome inhibitor and rituximab naïve.

Patients and Methods

Twenty patients with symptomatic WM were enrolled on this study and are assessable for response. Sixteen patients were previously untreated; four patients received prior therapy with everolimus on a clinical trial (3 non-responders, 1 with progressive disease). Therapy consisted of intravenous carfilzomib 20 mg/m2 for the first cycle, then 27 mg/m2 on subsequent cycles which was given on days 1,2,8,9, along with intravenous dexamethasone 20 mg given on days 1,2,8,9, and rituximab 375 mg/m2 given on days 2,9 of each cycle. Each cycle was 21 days for the 6 cycles of induction therapy. Responding patients were eligible for maintenance therapy which began 8 weeks after completion of induction therapy, and was given every 8 weeks for a total of 6 cycles that consisted of carfilzomib 27 mg/m2 on days 1,2; dexamethasone 20 mg on days 1,2, and rituximab 375 mg/m2 on day 2. Patients with IgM level >4,000 mg/dL underwent prophylactic plasmapheresis and/or had rituximab held while being treated on protocol until their IgM <4,000 mg/dL in order to prevent a rituximab-induced IgM flare. Patients received acyclovir (400 mg po BID) for shingles prophylaxis for the duration of protocol therapy plus 6 additional months from completion of carfilzomib, along with famotidine 20 mg po BID during active therapy.

Results

Six patients required prophylactic plasmapheresis for having IgM >4,000 mg/dL at baseline. The median number of treatment cycles administered to date is 6 (range 3-8), including maintenance. Median IgM levels declined from 3,375 to 1,314 mg/dL ($p<0.0001$), and hematocrit increased from 30.7% to 34.1% ($p=0.0067$). Among evaluable patients, median bone marrow disease involvement declined from 60% to 27% ($p=0.029$), The overall response rates and major response rates were 75% and 50% with one very good partial response, 9 partial responses, and five minor responses. The median time to attainment of at least a minor response for responders was 2 (range 1-3) months, and time to best response was 4 (range 2-9) months. With a median follow-up of 5 months, 14 of 20 patients remain on protocol therapy, and are free of disease progression. Overall, treatment was well tolerated and no patient came off study for toxicity. Grade $\geq$2 toxicities that possibly were related to protocol therapy were as follows: hyperglycemia (dexamethasone; n=10 , 50%); asymptomatic elevation lipase (carfilzomib; n= 7 , 35%); hypersensitivity (rituximab; n=6 , 30%); azotemia (carfilzomib; n= 2 , 10%) ; asymptomatic hyperbilirubinemia (carfilzomib ; n=1, 5%); anemia (carfilzomib; n=1 , 5%); neutropenia (carfilzomib; n=1, 5%); fatigue (dexamethasone; n=1 , 5%) . All toxicities were reversible, and no grade $\geq$2 peripheral neuropathy was observed. Two patients had rituximab truncated for hypersensitivity, and continued to receive carfilzomib and dexamethasone. Two patients had their carfilzomib dose reduced for asymptomatic, but recurring elevations in lipase. A rituximab related flare was observed in 2 (10%) patients, and was asymptomatic.

Conclusions

The results demonstrate that CARD is an active regimen in symptomatic patients with WM and produces rapid responses. Treatment is well tolerated and sparing of peripheral neuropathy on the current dose and schedule. Accrual and administration of treatment for this study is ongoing, and will be updated at the meeting.