[ABSTRACT WM2.3]

RITUXIMAB ALONE OR IN COMBINATION IN THE FRONTLINE TREATMENT OF WALDENSTROM'S MACROGLOBULINEMIA

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Waldenstrom's macroglobulinemia (WM) is a low grade lymphoplasmacytic lymphoma that is characterized by the production of a monoclonal immunoglobulin (IgM). The malignant lymphoplasmacytic cells are of B cell origin and while expression of some cell surface antigens is variable, CD20 expression on the malignant clone is nearly ubiquitous, making this surface marker an ideal candidate for targeted monoclonal antibody therapy. Rituximab is a chimeric monoclonal antibody against CD20 that is known to be effective in B cell lymphomas. Based on encouraging preliminary reports documenting clinical activity of rituximab in patients with refractory or relapsing WM, Dimopoulos *et al.* published the first prospective trial of single agent intravenous rituximab 375 mg/m2 given weekly for 4 weeks (in patients without progressive disease at 3 months this was also followed by 4 additional weekly doses of rituximab) to newly diagnosed patients with macroglobulinemia.1 Among 27 symptomatic patients with WM, 15 were previously untreated. Forty percent of these newly diagnosed patients achieved partial response (PR) characterized by ≥ 50% reduction in both monoclonal protein/tumor infiltration at involved sites. The median time to response for all patients (newly diagnosed+previously treated) was 3.3 months and only 3 patients had progressed at publication. The authors also described a transient, rapid increase of Mprotein in some responding and non-responding patients that occurred 15-30 days after initial treatment, followed by a gradual decrease in this level. This phenomenon, since referred to as an *IgM flare* is not necessarily indicative of treatment failure, and has also been reported after treatment with cladribine.2 One of three patients with neuropathy had improvement with regression of lymphoma (2 stabilized) and 1/1 patient with cold agglutinin anemia responded to therapy. Several prognostic factors were analyzed; patients with M protein < 40 g/L were more likely to respond (p.03) and there was a trend towards improved response in patients with a kappa light chain (p.19). Toxicity was mild, with immediate infusional reactions noted most frequently, and 4 infectious episodes noted at some point prior to progressive disease (zoster, erysipelas, bronchitis, and UTI). Simillar results were noted in a trial of extended rituximab therapy (375 mg/m2 IV weekly during weeks 1-4 and 12-16).3 Twelve previously untreated patients were included in a study of 29 patients that resulted in an overall PR rate of 48.3%, overall MR rate of 17.2% (response was not reported separately for previously untreated patients) and median TTP for untreated patients of 17 months. For both untreated and previouslytreated patients, response was only noted in 20% of 5 patients with IgM > 6000 mg/dL. A correlative study performed in these patients also evaluated whether expression of complement resistance antigens CD46, CD55, and CD 59 differed at baseline and post-treatment with rituximab. The only significant finding was on analysis of mean fluorescence Intensity (MFI) of CD55 expression after treatment with rituximab. Baseline MFI of CD55 revealed no significant differences between responding and nonresponding patients, however, after treatment, a significant increase in CD55 MFI was noted in 4/4 nonresponding pts compared with no difference in 7 responding patients (p.0006). If confirmed, these results suggest that targeted therapy, aimed at CD55 antigen expression, is worthy of study. In an attempt to clarify prognostic factors for successful rituximab therapy of WM, a retrospective review combined data from 23 previously untreated patients who received standard dose rituximab in 2 prospective trials from the University of Athens and MD Anderson Cancer

Center.4 The response rate of 35% was similar to that in the aforementioned study (Dimopoulos *et al.*) and the median TTP was 12.6 months. Multivariate analysis identified a monoclonal protein of ≥ 40 g/L and serum albumin < 35 g/L as significant predictors of TTP. Thus, 3 risk groups were developed based on these results; patients with both of these risk factors had the shortest median TTP (3.6 months), patients with neither risk factor had a long median TTP of >40 months, and, as expected, patients with one risk factor had an intermediate risk of progression of 11.1 months. More recently some of the same authors reported a study of 35 previously untreated patients with WM who received extended rituximab (as described above). 5 An overall response (OR) of 43% was reported, and after a median follow-up of 43 months, 19 patients progressed (5/15 responders) with a median progression free survival (PFS) of 23.6 months for all patients (not reached for responding patients). While patients with a higher albumin and lower M protein and those with hemoglobin > 10 g/dL and a kappa light chain were noted to have a higher frequency of response, Univariate analysis indicated that hemoglobin > 10g/dL was the single most important factor predicting a long PFS (median 57.5 months Vs 5.4 months). Other factors associated with longer PFS are consistent with previous reports and included albumin > 3.5 g/L (median 25.5 vs. 5.3 months), M protein < 4g/L (48mos vs. 6.2 months), absence of hyperviscosity (23 months vs. 3.5 months), and kappa light chain type (25.4 vs. 5.1 months). In a multicenter Phase II trial of standard dose rituximab.6 Twelve of 34 (35.3%) evaluable untreated patients had ≥PR, another 17.6% achieved MR and only 17.6% had disease progression. The median duration of response was 27 months and only 1 patient had died by the time of publication. In contrast to the aforementioned studies, pretreatment hemoglobin and monoclonal IgM level were not predictive of response (no similar analysis was performed for PFS). Grade 3-4 toxicities were infrequent, but included metabolic/electrolyte disturbances (glucose, calcium, potassium, magnesium and sodium) and known infusion related toxicities. Based on the significant single agent activity of rituximab in untreated WM, several investigators have reported significant activity of the antibody in combination with nucleoside analogues, alkylating and novel agents. We previously reported a program of 2-chlorodeoxyadenosine (2-CdA) 1.5 mg/m2 sc tid x 7d, cyclophosphamide (Cy) 40 mg/m2 po bid x 7d and rituximab (Rit) 375mg/m2 iv q wk x 4 wk (repeated at 6wks)(18 patients).7 Updated results (median follow-up, 68.5 months) reveal an overall response (>PR) of 94% (17% achieved CR), median time to remission was 2.4 months (2-CdA-Cy-Rit), and duration of first remission was 58.6mos, which appears better than the 25..6 months historically noted after treatment with the identical program without rituximab.

We also evaluated time to retreatment (TTRT) since many patients remain asymptomatic and do not require retreatment at the time of relapse. Median TTRT has not yet been reached (only 1 patient required retreatment), but appears improved compared with the same program without rituximab (56.3 months w/2-CdA-Cy, p=0.02). Similar results have been noted with cyclophosphamide-rituximab and other nucleoside analogs like pentostatin and fludarabine, but inclusion of previously untreated patients with WM remains limited (< 6 pts each). One concern has been the difficulty with stem cell collection in patients after treatment with 2-CdA and thus the role of rituximab in other combinations is of particular interest. Dimopoulos *et al.* reported the primary treatment of 60 patients with WM given cyclophosphamide 100mg/m2 po bid on d1-5 and dexamethasone 20 mg IV followed by ,rituximab 375 mg/m2 IV on d1, repeated q21d x 6.8 Seventy percent of patients (63%PR, 7%CR) responded and PD was noted in only 10%. .At a median follow-up of 24 months, 60% of patients remain progression free. Twenty percent of patients experienced g3-4 neutropenia. Since stem cell collection was

possible in all patients in whom it was attempted, this regimen shows particular promise for primary treatment of WM. Preliminary results of a program of bortezomib 1.3 mg/m2 IV and dexamethasone 40 mg IV on days 1,4,8,11 and rituximab 375 mg/m2 on d11 x 4 cycles (repeated after 3 months) in 10 evaluable patients have recently been presented.9 Response was rapid (median 1.1 months) and all patients achieved at least a minor response and 50% achieved at least PR. The program was well tolerated (no neuopathy has occurred), but because 40% of patients developed herpes zoster, valacyclovir prophylaxis has been added. The same author recently reported results combining the novel agent lenalidomide (25 mg/d po x 21d repeated q 28d x a total of 48 weeks) with rituximab.(375 mg/m2/wk, wks 2-5, 13-16) in 10 untreated patients (12pts total).10 Eighty-five percent of patients had an acute hematocrit decrease (median 4.2%) and toxicities of myelosuppression and IgM flare (requiring pheresis, 2 pts) were also noted. Although 3/8 evaluable patients achieved PR and 4/8 patients achieved MR, 8/12 patients discontinued treatment. While the results are promising, the ideal dose and schedule for this regimen remain unclear. These trials demonstrate significant activity of rituximab for primary therapy of WM. While this drug should be used judiciously as a single agent in patients with high levels of circulating IgM (to avoid flare-related hyperviscosity), its greatest use may be in patients with marrow hypocellularity or for those in whom stem cell collection is warranted. Preliminary results, however, indicate that the addition of rituximab to combinations of chemotherapeutics/novel agents results in high response rates and durable remissions even after limited therapy, indicating this agent is likely to continue to play a significant role in primary therapy for Waldenstrom's macroglobulinemia.

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