

[Abstract 40]

THALIDOMIDE AND RITUXIMAB IN WALDENSTRÖM'S MACROGLOBULINEMIA

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Rituximab and thalidomide are active agents in Waldenstrom's macroglobulinemia (WM) producing major response rates of 25-50%. Moreover, as previously shown by us, thalidomide enhances rituximab mediated ADCC killing of lymphoplasmacytic cells (Blood 100:314b). As such, we conducted this phase II study using combination rituximab and thalidomide in WM patients who previously had not received rituximab or thalidomide. Intended therapy was as follows:

Weeks 1-52 Thalidomide (200 mg po qhs for 2 weeks, then 400 mg po qhs)
Weeks 2-5 Rituximab (375 mg/m²/week)
Weeks 13-16 Rituximab (375 mg/m²/week)

Patients were evaluated at week 12, and if they had at least stable disease (SD) were eligible for further therapy and for response evaluation. Dose modifications, delay, and/or discontinuation of thalidomide were permitted for toxicities. Twenty-five patients have been enrolled, 20 of whom were previously untreated. Six patients are off study, 4 because of no response and 2 because of deaths unrelated to protocol therapy. Grade 3/4 toxicities to thalidomide included neuropathy (n=15); somnolence or confusion (n=12); rash (n=7); tremors (n=2); bradycardia (n=2); other (n=3); and led to its eventual discontinuation in 11/19 patients. All evaluable patients received the intended rituximab therapy. Paradoxical IgM spikes following rituximab occurred during both courses of therapy and were observed in 12/25 (48%) patients similar to those spikes which we reported with rituximab monotherapy (ASH 2003; 102:690a). Responses to date among the 23 evaluable patients are as follows: CR (n=1); PR (n=12); MR (n=2); SD (n=4). Four patients had no response to therapy. No patients with stable disease or better have progressed with a median follow-up of 10 months (range 6-13 months). Response to therapy is associated with cumulative dose of thalidomide. Patients who responded to therapy received a median thalidomide cumulative dose of 37,600 (range 5700-74,500) mg as compared to 5,650 (range 2100-21,000) mg among non-responding or stable disease patients. These studies demonstrate that thalidomide in combination with rituximab is active in WM, and associated with the cumulative dose of thalidomide. In view of the encouraging response rates obtained with this combination and the potential for improved toxicity profile, a phase II study examining the thalidomide analogue CC-5013 (Revlimid) plus rituximab has been initiated.