[ABSTRACT WM3.8]

Use of the immunomodulators thalidomide and lenalidomide to augment rituximab clinical activity in Waldenstrom's Macroglobulinemia

Soumerai J. (1), Branagan A. (1), Hunter Z. (1), Patterson C. (1), Hatjiharissi E. (1) and Treon S. (1)
Bing Center for Waldenstrom's Macroglobulinemia, Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts, USA.

Introduction: Rituximab is active in Waldenstrom's macroglobulinemia (WM), producing response rates of 30-40%. Lower response rates are observed among patients with Fc□RIIIA-158 FF polymorphism; high B_2M (≥3.0mg/dL), and high IgM levels (≥6,000mg/dL). We investigated two immunomodulators: Thalidomide and its analogue Lenalidomide in combination with Rituximab given previous studies demonstrating increased ADCC activity against lymphoplasmacytic cells (BJH 128:192; Cancer Res 65:11712).
Methods: We conducted 2 phase II clinical trials in symptomatic patients with the clinicopathological diagnosis of WM using consensus panel criteria. Intended treatment and patient characteristics were as follows:

	Thalidomide and Rituximab	Lenalidomide and Rituximab
Intended therapy:	Weeks 2-5, 13-16: Rituximab (375 mg/m^2/wk); Weeks 1-52: Thalidomide (200 mg po qHS for 2 wks, then 400 mg po qHS)	Weeks 2-5, 13-16: Rituximab (375 mg/m^2/wk); Weeks 1-48: Lenalidomide (25 mg po qD for 3 weeks, 1 week off)
Enrolled:	25	16
Previous therapies:	0 (0-1)	0 (0-2)
Age:	62 (44-86 yrs)	65 (49-85 yrs)
Serum IgM:	3,670 (924-8,610 mg/dL)	4,000 (1,180-7,130mg/dL)
Hct:	34.1 (23.6-42.6%)	32.1 (24-36.6%)
BM Involvement:	40 (5-80%)	37.5 (5-90%)
B2M:	2.6 (1.4-8.3 mg/L)	3.3 (1.8-6mg/L)

Results: In the phase II study of Thalidomide and Rituximab in WM, 23/25 patients were evaluable and responses included: CR (n=1); PR (n=15); MR (n=2); SD (n=1) for an overall (ORR) and a major response rate (MRR) of 78% and 70%, respectively. Median serum IgM levels decreased from 3,670 (924-8,610 mg/dL) to 1,590 (36-5,230 mg/dL) ($p<0.001$), while the median hematocrit rose from 33.0 (23.6-42.6%) to 37.6 (29.3-44.3%) ($p=0.004$) at best response. With a median follow-up of 42+ months, the median TTP for evaluable patients on study was 35 months, and 38+ months for responders. ORR was associated with median cumulative Thalidomide dose: CR/PR/MR (29,275 mg) vs. SD/NR (7,400 mg); $p=0.004$. ORR were unaffected by Fc□RIIIA-158 polymorphism (81% vs. 71% for VV/FV vs. FF); IgM (78% vs. 80% for <6,000 vs. ≥6,000 mg/dL); and B_2M (71% vs. 89% for <3 vs. ≥3 g/dL); p=NS. Dose reduction of Thalidomide occurred in all patients and led to discontinuation in 11 patients. Among 11 patients experiencing grade ≥2 neuroparesthesias, 10 demonstrated resolution to grade 1 (n=3) or complete resolution (n=7) at a median of 6.7 (range 0.4-22.5 months).
In our phase II study of Lenalidomide and Rituximab in WM, 12/16 patients were evaluable and responses included: PR (n=4); MR (n=4); SD (n=3); NR (n=1) for an ORR and MRR of 67% and 33%, respectively, with a median TTP of 15.6 months. In two patients with bulky disease, significant reduction in node/spleen size was observed. Acute decreases in hematocrit were observed during first 2 weeks of Lenalidomide therapy in 13/16 (81%) patients with a median hematocrit decrease of 4.4% (1.7-7.2%), resulting in hospitalization in 4 patients. No evidence of hemolysis or more general myelosuppression was observed in these patients.

Conclusions: Thalidomide in combination with Rituximab is highly active, produces long-term responses, and may overcome unfavorable prognostic determinants previously reported with Rituximab monotherapy in WM. The use of Thalidomide along with Rituximab appears superior in efficacy, and better with regard to tolerability versus those observed with Lenalidomide and Rituximab in a similar clinical population of patients with WM.