Prospective, multicenter clinical trial of everolimus as primary therapy in Waldenström macroglobulinemia

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Background

Everolimus (RAD001) is an inhibitor of MTORC1, a component of the Akt-MTOR pathway which regulates growth and survival of lymphoplasmacytic cells in Waldenstrom's Macroglobulinemia (WM). Everolimus also exhibits activity in WM patients with relapsed/refractory disease (Ghobrial et al, JCO 2010; 28:1408-14). We therefore initiated this multicenter, prospective study to delineate the efficacy and tolerability of Everolimus as primary therapy in WM.

Methods

We evaluated everolimus in a prospective, multicenter study of 33 symptomatic, previously untreated WM patients. Intended therapy consisted of everolimus (10 mg/day) until progression or unacceptable toxicity. Dose reduction was permitted to as low as 5mg QOD. The primary endpoint was determination of overall response rate. Secondary endpoints included determination of time to progression, and assessment of safety and tolerability of everolimus. The study was registered at www.clinicaltrials.gov (NCT01470196).

Results

Table 1. Baseline Characteristics of the Patients

Characteristic Patients (N=33)	Baseline (n=33)	Post-Everolimus
Age of treatment initiation – yr	62 (41-80)	n/a
Hemoglobin – g/dL	10.8 (7.8-15.7)	11.8 (8.7-15.5)
Serum IgM – mg/dL	4,440 (959-10,256)	1,360 (146-7,280)
M-spike –g/dL	2.60 (0.31-5.31)	0.93 (0-4.31)
MYD88 L265P n=21	95.2 (20)	n/a
CXCR4 WHIM n=21	19 (4)	
Bone marrow involvement - %	70 (1.65-95)	40 (0.75-100)

Results

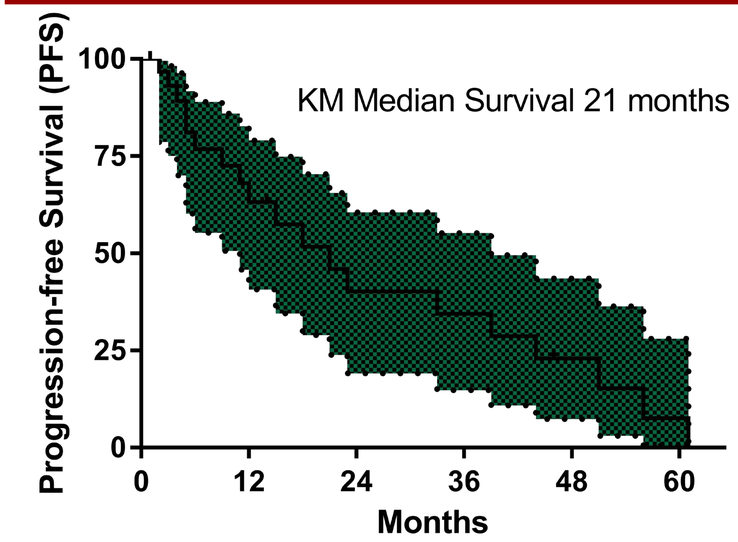

Figure 1: Progression-Free Survival

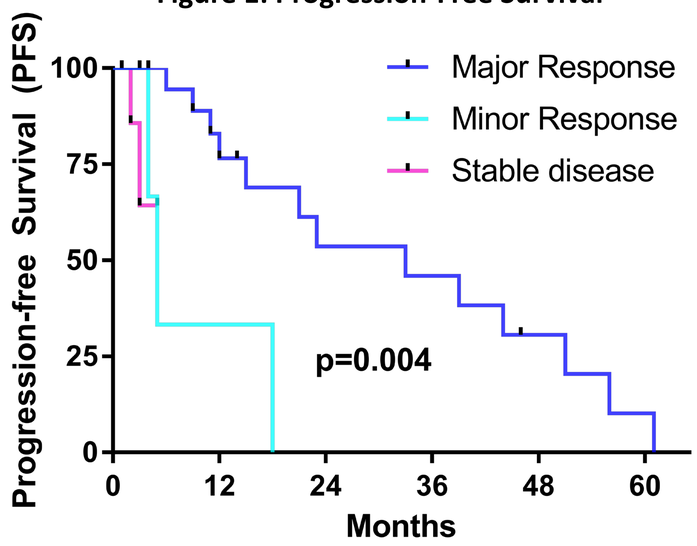

Figure 2: Progression-Free Survival by Best Response

The median number of treatment cycles administered was 9 (range 1-64)

Results

At best response, median serum IgM levels declined from 4,440 to 1,360 mg/dL ($p<0.0001$); median hemoglobin rose from 10.8 to 12 g/dL ($p=0.001$); and median bone marrow disease burden declined from 75% to 52.5% in serially biopsied patients. The ORR and major response rates were 72.7% and 60.6%, respectively. Among genotyped patients, non-responders associated with wild-type MYD88 and mutated CXCR4 status. Median time to response was 4 weeks. Discordance between serum IgM levels and BM disease burden was common. With a median follow-up of 12 (range 1.6-65 months), median time to progression was 21 months, and 33 months for major responders. Discontinuation of everolimus led to rapid serum IgM rebound in 7 patients, and symptomatic hyperviscosity in two patients. Toxicity led to treatment discontinuation in 27% of patients, including 18% for pneumonitis.

IgM and Bone Marrow Responses to Everolimus Therapy

	Overall response rate	Major response rate	VGPR	PR	MR	SD/PD
Serum IgM response (consensus criteria) (n=33)	72.7%	60.6%	1	19	4	11
Bone Marrow response (n=27)	40.7%	33.3%	0	9	2	16

Conclusion

Everolimus is active as a primary therapy in WM. IgM discordance is common, and treatment cessation can often lead to rapid serum IgM rebound. Pneumonitis also appears more pronounced in untreated versus previously treated WM patients. The risks and benefits of everolimus should carefully be weighed against other primary WM therapy options.