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To the editor:

Once- versus twice-weekly bortezomib induction therapy with CyBorD in newly diagnosed multiple myeloma

After observing high response rates in relapsed multiple myeloma (MM) patients,[1] we examined a 3-drug combination of bortezomib, cyclophosphamide, and dexamethasone (CyBorD) in newly diagnosed symptomatic patients. This phase 2 trial was open at Mayo Clinic Arizona and Princess Margaret Hospital, Toronto, was approved by the institutional review board/research ethics board of both centers, and was monitored by the Mayo Clinic Cancer Center Data and Safety Monitoring Board. Eligibility requirements were age 18 years or older, Eastern Cooperative Oncology Group performance status less than or equal to 2, Creatinine less than 3.5 mg/dL, absolute neutrophil count 1000/μL or more, platelets 100 000/μL or more, and informed signed consent. Patients had to have measurable disease. The primary end point of the study was confirmed response after 4 cycles (16 weeks). Responses were assessed according to modified EBMT criteria.[2]

The first 33 patients (cohort 1) received 300 mg/m^2 of cyclophosphamide by mouth on days 1, 8, 15, 22, 1.3 mg/m^2 of bortezomib intravenously on days 1, 4, 8 and 11, and 40 mg of dexamethasone by mouth on days 1 to 4, 9 to 12, and 17 to 20. As we reported,[3] the ORR (≥ PR) was 88%, with 61% VGPR or better. High-dose dexamethasone and bortezomib can both be associated with toxicities, treatment delays and discontinuation which may limit efficacy. To maximize dose delivery and reduce toxicity, we modified the original schedule and accrued 30 additional patients: cohort 2 received the same weekly cyclophosphamide schedule, 1.5 mg/m^2 of bortezomib intravenously on days 1, 8, 15, 22, and dexamethasone as in cohort 1 for cycles 1 and 2, then 40 mg once weekly for cycles 3 and 4.

Table 1. Overall response

ITT	Cohort 1 (n = 33)	Cohort 2 (n = 30)	All (n = 63)
ORR	88%	93%	90%
CR/nCR	39%	43%	41%
VGPR or better	61%	60%	60%
After 4 cycles	(n = 28)	(n = 27)	(n = 55)
ORR	96%	93%	95%
CR/nCR	46%	48%	47%
VGPR or better	71%	63%	67%
Toxicity			
Any ≥ Gr 3 AE	48%	37%	
Gr ≥ 3 Thrombocytopenia	21%	0%	
Gr ≥ 3 Neutropenia	12%	7%	
Gr ≥ 3 Anemia	9%	0%	
Gr ≥ 3 PN	6%	0%	
Any Gr PN	64%	57%	
Bortezomib doses reduced	21%	13%	
Dex dose reduced	30%	20%	

ITT indicates intention to treat; ORR, overall response; CR, complete response; nCR, near complete response; VGPR, very good partial response; GR, grade; AE, adverse event; and PN, peripheral neuropathy.

The trial required 30 patients in each cohort to test the null hypothesis that the true success proportion in this patient population is at most 20%.

Cohort 1 had more International Staging System stages II/III than cohort 2 (67% vs. 44%) but cohorts were otherwise comparable. The overall response (≥ PR) for all 63 patients is 90% with 41% CR/nCR and 60% VGPR or better (Table 1). For those completing all 4 cycles of therapy (n = 55), the ORR is 95% with 47% CR/nCR and 67% VGPR or better. Patients in the once weekly bortezomib cohort achieved responses similar to the twice weekly cohort (ORR 93% vs 88%, ≥ VGPR 60% vs 61%) and experienced less grade 3/4 adverse events (37%/3% vs 48%/12%). Fewer dose reductions of bortezomib and dexamethasone were required in the modified schedule and neuropathy rates were the same in both cohorts even though the total bortezomib dose per cycle was higher in the weekly versus the twice weekly schedule (6.0 mg/m^2 vs 5.2/mg/m^2).

CyBorD is a highly efficacious regimen and arguably as active as any 2- or 3-drug regimen reported to date.[4-7] We have had the ability to study 2 different dosing schedules of this combination and have shown both to be very active but one appears less toxic and is more convenient for the patient. A prospective, randomized, clinical trial to confirm these results seems warranted. The weekly bortezomib dosing with low-dose dexamethasone has become our preferred induction regimen for transplant eligible patients.

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