

PBSCs after PAD, with secondary objectives being assessments of safety, toxicity, response rate (RR), PFS and OS.

Methods

Patients with previously untreated MM were eligible. Patients were treated with 4x21 day cycles of PAD comprising bortezomib 1.3 mg/m² on days 1,4,8 & 11 along with 40 mg dexamethasone on days 1-4, 8-11 & 15-18 during cycle 1 and days 1-4 during cycles 2-4. During days 1-4 of each cycle, patients also received 0 mg/m², 4.5 mg/m² or 9 mg/m² of adriamycin at levels 1, 2 & 3 respectively. Following harvesting, patients received high dose melphalan (MEL200) with stem cell (PBSC) rescue. Gene expression profiling was performed on purified plasma cells from diagnostic samples for

pharmacogenomic analysis.

Results

Thus far, 21 patients have been enrolled (19 male 2 female, median age 55 years [range 36-66]). All 21 have completed PAD with a 95% PR/CR rate. 20/21 patients mobilised PBSC successfully (median collection 3.8 x 10⁶ CD34+ cells/kg, range 1.6-10.4). 16 patients have received MEL200 with median neutrophil (>0.5 x10⁹/L) and platelet engraftment (>20 x10⁹/L) of 15 (1-24) and 13 (10-33) days respectively. Of patients who are assessable at 3 months post MEL200, 11/12 have achieved at least a PR (CR 4, nCR 1, VGPR 4 & PR 2). Toxicities have generally been acceptable with 15 grade 3 events: 6 infections, 4 episodes of shingles, 2 nausea and vomiting, 2 neuropathy and 1 postural hypotension.

Overall, 48% of patients have experienced sensory or painful neuropathy which is of Grade 1 severity in 43% of cases. Of note, neuropathic symptoms are improving in all patients after completion of therapy.

Summary

These preliminary data show that PAD is well tolerated in the majority of patients, is highly effective and does not prejudice subsequent PBSC collection. A further cohort of patients will receive PAD with bortezomib at 1.0 mg/m² in order to determine whether the frequency of neuropathy can be reduced whilst preserving efficacy. PAD should be further evaluated as first line therapy in prospective randomised trials. *Abstract #1478 appears in Blood, Volume 104, issue 11, November 16, 2004 OA*

Phase II Trial of Single Agent Bortezomib (VELCADE®)

In Patients with Previously Untreated Multiple Myeloma (MM)

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Session Type: Oral Session (Abstract #336)

Introduction

Bortezomib, a first in class proteasome inhibitor, has become a standard of care in the treatment of relapsed and refractory MM. A recent randomized Phase 3 trial showed an improvement in time to progression (TTP) and overall survival relative to dexamethasone (dex) in patients with relapsed MM and 1-3 prior lines of therapy. In relapsed MM, the rate of treatment-emergent significant peripheral neuropathy (PN) with bortezomib was higher in patients with baseline neuropathy. The incidence and severity of PN in front-line treatment will be important to define. This multi-center, Phase 2 study was planned to evaluate the activity and toxicity (in particular PN) of single agent bortezomib in previously untreated pts.

Methods

Response rate, TTP, tolerability, incidence and severity of PN, and the effect of dose modification, symptomatic treatment and nutritional supplements on PN were

evaluated in previously untreated, symptomatic MM pts. Pts received bortezomib 1.3 mg/m² on D 1, 4, 8, and 11 of a 21-d cycle and response to treatment was assessed every 2 cycles. Dex was not permitted. Neurologic evaluation was required before and after treatment, and if significant PN developed during therapy.

Results

28 pts with symptomatic MM have been treated with a median age of 60 yrs, IgG isotype in 68% and Stage III disease in 52%. Analysis of best paraprotein response after ≥2 cycles revealed CR in 1 (5%) pt and PR in 8 (36%), for an ORR of 41% in 22 evaluable pts. An additional 5 pts (23%) achieved MR, with stable disease in 6 pts (27%); 2 pts progressed (9%). The most commonly reported adverse events included PN, fatigue, GI symptoms and rash. Neurological evaluation has been performed in all pts, including nerve conduction studies (NCS), assessment of autonomic function and skin biopsy for EM imaging of small fibers in a subset (n=19). Six of 28

pts (21%) so far have developed PN with most being G2: 1 pt experienced G3 PN and drug was discontinued. Dose modification was required in 4 pts and supplements have been used in all pts with PN. Preliminary results of neurological testing and NCS have indicated subclinical PN at baseline prior to therapy in 6/19 (30%) of pts evaluated by NCS, with small fiber, axonal PN documented in 1 pt with treatment-emergent PN. Bortezomib-related toxicity has otherwise been manageable.

Conclusion

Single agent bortezomib is a promising approach for newly diagnosed pts and is without the complications of high-dose dex. The incidence of subclinical PN by NCS at baseline prior to therapy is currently 30%; G2 or greater treatment-emergent PN has occurred in 21% of pts and was G3 in only 1 pt (4%) to date. Further assessment of PN including analysis of skin biopsies is ongoing. *Abstract #336 appears in Blood, Volume 104, issue 11, November 16, 2004 OA*