

First-line Therapy with Bortezomib

(Formerly PS-341) in Patients with Multiple Myeloma

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Background

Preclinical evidence has suggested that the proteasome is an effective therapeutic target in MM. Clinical trials have since demonstrated the durable efficacy and safety of bortezomib (Velcade), a potent reversible proteasome inhibitor, recently approved for the treatment of pts with refractory and relapsed MM. Preliminary results of an ongoing phase 2 trial of bortezomib administered to pts with newly diagnosed MM are reported here.

Methods

Pts received bortezomib 1.3 mg/m² 2x/wk x2 q3 wk for a maximum of 6 cycles. Dexamethasone 40 mg the day of and after each bortezomib dose was allowed after 2 cycles for pts with < PR, and after 4 cycles for pts with < CR. Response criteria were based on modified EBMT criteria, with the

addition of a near CR category (disappearance of all M protein by electrophoresis, but positive immunofixation, with normal bone marrow). Stem cells could be harvested at the discretion of the physician. Neurologic tests are being performed before and after bortezomib.

Results

Nineteen pts (47% males, median age 63 yrs) have been accrued. Pts presented with IgG (58%), IgA (32%), or light chain (10%) disease, with a median KPS of 90 (50 - 100). The majority of pts were Durie-Salmon Stage III (55%). As of November 2003, 12 pts have completed 6 cycles and were evaluable for response: there were 4 (33%) near CR, 5 (42%) PR, 1 (8%) MR, and 2 (17%) PD. One pt has undergone stem cell transplant with complete hematologic

recovery. The most common adverse events (grades 1 - 3) were fatigue (67%), diarrhea (58%), constipation (42%), nausea (42%), peripheral neuropathy (33%), and vomiting (33%). One episode of each of the following grade 3 events occurred: abdominal pain, diarrhea, dizziness, dyspnea, fever, neuropathic pain, neutropenia, syncope, and vomiting. One pt required dose modification. No grade 4 toxicity was observed.

Conclusions

In this study, bortezomib appeared to be promising as initial therapy in patients with newly diagnosed MM and had manageable toxicities. Major responses (near CR and PR) were seen in 75% of the patients by 6 cycles. Study accrual is ongoing, and the full complement of 42 pts is expected to be recruited quickly. **OA**

Source: ASCO, 2004 Annual Meeting

PAD Therapy for Untreated Multiple Myeloma

(Bortezomib, Doxorubicin and Dexamethasone)

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Background

Bortezomib (Velcade, formerly PS341) (P) shows encouraging clinical results in patients (pts) with relapsed MM with dexamethasone showing additive benefit. In vitro, P demonstrates potent synergy with cytotoxics including anthracyclines. Therefore, a Phase I/II study of PAD combination was undertaken in patients with previously untreated MM. The study objectives were: feasibility of peripheral blood stem cell (PBSC) collection and support for high dose melphalan (HDM); safety, toxicity and response rate.

Methods

Pts with previously untreated MM were eligible. Pts received 4x21 day cycles of PAD.

All pts received P 1.3mg/m² on days 1,4,8,11 and oral D 40mg days 1-4, 8-11, 15-18 Cycle 1 (day 1-4 only cycles 2-4). Level 1 pts received no doxorubicin [Adriamycin (A)], level 2 pts received 4.5mg/m² d1-4, level 3 received 9mg/m² d1-4. Following PBSC harvesting, HDM with PBSC rescue was given. In vitro testing included gene expression analysis on purified plasma cells to identify gene expression profiles associated with response and known prognostic factors.

Results

Fifteen pts are enrolled (1F; median age 52 [37-64] yrs) and all have completed at least 1 cycle (Level 1 - 3 pts; level 2 - 4 pts; level 3 - 8 pts). All pts have achieved at least a partial response with 2 achieving a complete

response by immunofixation (1 at level 1; 1 at level 3). In 8/8 pts PBSC collection was successful (median 3.13 x10⁶ CD34+ cells/kg (1.92-7.4). 6 pts have completed HDM with PBSCs. Median time to neutrophil (>0.5) and platelet (>20) engraftment was 18 days (13-23) and 12.5 days (10-33). Most adverse events were NCI-CTC Grade 1-2. Of 6 serious adverse events only 2 were considered to be possibly study drug related. There were no deaths on study.

Conclusion

PAD is well tolerated, highly effective and does not prejudice PBSC collection or subsequent engraftment. PAD warrants further evaluation in prospective clinical trials. **OA** Source: ASCO, 2004 Annual Meeting