Research Article

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Bone Effect of Low Dose Bortezomib in Patients with Relapsed/Refractory Multiple Myeloma

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Abstract

Bone disease in myeloma patients result from the exaggerated osteoclast activity and suppression of osteoblast function in the myelomatous bone marrow and is responsible for most serious complications of myeloma. The bone anabolic effects of bortezomib with 1.3 mg/m^2 and 1 mg/m^2 dosages have been previously reported. In this study, we for the first time examined the effect of Bortezomib 0.7 mg/m^2 dose on bone metabolic parameters in six patients with relapse MM. Even with the low dose used in the trial, we observed increase in the PTH levels in 50% of treated patients and parallel changes in osteocalcin levels, suggesting osteoblastic activation. To our knowledge, this is the first report of bone anabolic effects of bortezomib associated proteasome inhibition at such small doses.

Keywords: Multiple myeloma; Hematological malignancy; Bortezomib bone

Introduction

Multiple myeloma (MM) accounts for approximately 1% of all malignancies and 10% of hematological tumors, representing the second most frequently occurring hematological malignancy in the United States [1]. Bone disease in myeloma patients result from the exaggerated osteoclast activity and suppression of osteoblast function in the myelomatous bone marrow. Presently, the treatment of the bony complications of myeloma primarily involves induction of apoptosis of osteoclasts. In addition, bisphosphonates have been shown to inhibit stromal production of cytokines such as IL-6 and may alter tumor cell adhesion to stroma [2]. Bone disease is responsible for the most severe complications associated with multiple myeloma. As treatment and survival of myeloma patients improve, new therapies that directly stimulate bone formation, increase bone mass, and improves the quality of life of myeloma patients are vitally needed.

Materials and Methods

Six patients with documented progressive multiple myeloma were enrolled into the study over the period of 18 months. This single arm phase II exploratory study prospectively evaluated the effect of Velcade at 0.7 mg/m^2 dose, given in short course (i.e. 3 cycles) on inducing osteoblast activation as measured by ALP and other bone markers such as PTH in patients with relapsed/refractory myeloma.

The secondary aim of the study was to evaluate the association between osteoblastic activation, myeloma response to Velcade in terms of disease progression and to identify predictive factors for Velcade-associated osteoblastic activation.

Bortezomib was administered as a single agent in 3-5 second bolus IV injection at the dose of 0.7 mg/m^2 on days 1, 4, 8, and 11 q. 21 days times three cycles. The use of bisphosphonates was not allowed during the study period.

Differences in bone markers (PTH, osteocalcin, ionized calcium, phosphorus, alkaline phosphatase) between different myeloma responses were evaluated using median and median percent difference from baseline values.A median two sample test was used to determine point wise differences within the 3 cycles. Smoothed spline plots will be used for visual comparison of responder category across all 3 cycles. Pre and post dose values for architectural parameters will be used to compare responders and non-responders via paired t-tests. The protocol was approved by ethical committee of the University of Utah (Protocol number-X05308/IRB #35813). Written consent was obtained from each patient.

Results

Six patients were enrolled in the study; with a median age of 69 yrs, 3 patients were IgG isotype, 1 was IgA isotype and two were kappa light chain myelomas. The baseline risk characteristics did not reveal abnormality on interphase FISH and none of the patients had 17p deletion at diagnosis or at the time of enrollment into study. All the patients experience relapse after autologous transplant and had received previously exposed in the course of the disease to proteasome inhibitor drugs and IMiDs. 5 patients had received single agent high dose Melphalan as a conditioning regimen, while one patient received BEAM as conditioning prior to auto-HCT. Post auto-transplant, 4 patients had received maintencance treatment for variable time period ranging 1 to 2 years. The changes in bone marrow plasmacytosis at baseline and the end of study are summarized in the table below (Table 1).

Patient No	Baseline		BM after treatment	
	Asp %PC	Bx %PC	Asp %PC	Bx %PC
1	47.7%	50.0%	38.8%	50.0%

2	7.6%	50% k	10.0%	7.5% k
3	6.8%	20% λ	28.8%	80% λ
4	32.4%	50% k	60.4%	90% k
5	30.8%	50% k	35.5%	60% k
6	5.4%	5% m	4.8%	20% k

Table 1: Bone marrow plasmacytosis at baseline and after treatment. (Asp: Aspirate, Bx: Biopsy).

All patients received 0.7 mg/m^2 of bortezomib on days 1, 4, 8 and 11 of a 21-day cycle, for a maximum of three cycles. 1 patient developed progressive disease after 2 cycles and hence the patient was taken off protocol. 1 patient showed disease progression after completion of the 3 cycles. 4 patients had stable disease.

Increase in alkaline phosphatase, serum ionized calcium and PTH levels were observed during study period at the end of first cycle. Small differences in median baseline and end of study bone marker values in three of the four bone markers were recorded. Phosphorous levels increased by 0.22 mg/dL, Ionized Calcium increased by 0.06 mmol/L, and Osteocalcin increased by 0.58 ng/mL. During the first day of the treatment, 3 out of 6 patients experienced a PTH rise of >30%. Those individuals experienced stable disease. 2 out of 3 patients with negative changes in serum PTH experience progressive disease. Table 2 shows the values in maximum absolute percent change in PTH from baseline on the first day of treatment.

Patient	%
1	113.5
2	-9.09
3	30.7
4	-50
5	93.6
6	-53.5

Table 2: Percent change in PTH from baseline.

Discussion

Myeloma is the prototype of hematological malignancy associated with bone disease. Lytic bone disease is responsible for the most debilitating manifestations of the disease, including bone pain and fractures.

Lytic bone disease is typically absent in MGUS and smoldering myeloma, but is present in overt myeloma in 80% of cases [3]. Bony changes proceed by 3 years from the development of over myeloma.

Histologic studies of bone have revealed excessive bone resorption in the vicinity of the myeloma cells, with severe inhibition of bone formation [4,5]. Once myeloma cells invade the bone marrow, they adhere to the stromal cells and induce secretion of osteoclast-activating factors, including interleukins 6, MIP 1α and IL-1ß and tumor necrosis factor-ß. These factors prompt the stromal cells and osteoblasts to secrete tumor necrosis factor-related induced cytokine, or RANKL, a member of the tumor necrosis factor family, which induces differentiation and maturation of osteoclast progenitors [4-6]. Unchecked osteoclastic activity promotes the production and release from stromal cells of various cytokines, which lead, directly or indirectly, to further MM clone proliferation. A vicious cycle, with bone destruction "feeding" tumor growth and MM cells promoting bone destruction, is therefore set in motion. This set of factors leads to the common findings in MM: sever osteopenia and multiple spinal compression fractures [4].

The increased production of RANKL by the bone marrow stroma, and decreased osteoprotegerin (OPG) is a common finding in myeloma [5]. OPGis produced by the bone marrow stromal cell and function as a decoy receptor for RANKL, preventing binding to RANK on osteoclasts [6].

Anabolic activity of bortezomib is associated with increased the activity of the critical osteoblast transcription factor, RUNX2, in human osteoblast precursors and stimulated bone nodule formation in vitro [7]; which was associated to an increase in the number of osteoblasts per mm^2 of bone tissue and the number of RUNX2 positive osteoblastic cells.

Bortezomib is known to decrease DKK1 and RANKL concentrations with normalization of bone remodeling [8].

We have previously reported the Bortezomib associated changes in serum intact PTH levels in patients treated with 1.3 mg/m^2 and 1 mg/m^2 dosages [9].

This study for the first time has examined the effect of Bortezomib 0.7 mg/m^2 dose on bone metabolic parameters in patients with relapse MM. Even with the low dose used in the trial we observed, increase in the PTH levels in 3 patients. Those patients with negative changes in PTH from the baseline levels experienced progressive disease. Parallel changes in the osteocalcin levels also changed during treatment supported osteoblastic activation. Phosphorous levels changed significantly during treatment with median increase of 0.8 mg/dL to 1.1 mg/dL in 3 patients who had reached stable disease.

This limited study supports that significant changes in bone metabolic and hormonal markers can be observed even during low dose bortezomib treatment.

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