A new spectrum-selective cathepsin inhibitor, VBY-825, inhibits bone destruction in a syngeneic 5TGM1 multiple myeloma mouse model

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Introduction
Multiple myeloma (MM) is the second most common blood cancer after non-Hodgkin lymphoma. It is a monoclonal B-cell neoplasia with clinical hallmarks of multiple osteolytic lesions causing bone pain, fractures and hypercalcemia. Certain treatments, such as chemotherapy or radiotherapy, may induce remissions, but MM is generally thought to be incurable, and therefore new treatment options are desperately needed. Protelodysic activity is required for several key processes in malignant progression of cancer. Members of the cathepsin protease family are implicated in tumor invasion and metastases. VBY-825 is a novel spectrum-selective cathepsin inhibitor, which has high potency against cathepsins K, L, B, S and V.

Materials and Methods
5TGM1 cells were inoculated into the tail vein of 7 weeks old female C57BL/KaLwRj mice. Mice (n = 48) were randomized to 4 groups: Control group receiving vehicle of test compound (5% dextrose 10 ml kg daily) (vehicle 1); control group receiving vehicle of bortezomib (3 ml kg twice a week) (vehicle 2); reference group receiving bortezomib (0.1 mg kg twice a week) which is a FDA approved drug for MM; reference group receiving VBY-825 (100 mg kg daily). Administration of all compounds began one day after tumor cell inoculation and continued until day 34. Disease progression was followed by measuring the levels of paraproteinemia, serum parameters, TRACP 5b in serum, radiography and weighing the mice. The mice were sacrificed 5 weeks after inoculation, examined macroscopically, and their bones were collected for histomorphometric analysis.

Our aim was to observe the effects of a cathepsin inhibitor VBY-825 on bone lesions and tumor burden in the syngeneic 5TGM1 mouse MM model using immunocompetent C57BL/KaLwRj mice.

Results

Histomorphometric analysis

FIGURE 3. A: Trabecular bone area (mm², median [Q25-Q75] [horizontal bar]) was determined histomorphometrically. Statistically significant changes were not observed, but there was a trend (p = 0.037) of increased osteolytic bone area in the VBY-825 treated group. B: The number of osteoclasts at tumor-bone interface (k/mm). Number of osteoclasts in tumor-bone interface increased in VBY-825 treated animals. C: Representative images of the Masson-Goldner trichrome stained histological sections. * p < 0.01, NS = Non-significant.

Biochemical markers

FIGURE 4. A: Total osteocalcin at sacrifice (ng/mL, median [Q25-Q75] (horizontal bar)) was determined from x-ray radiography. Bortezomib and VBY-825 decreased total osteocalcin area. \* = p < 0.05. B: Representative x-ray images of each treatment group visualizing also the analysis of osteolytic lesions. Each polygon represents one lesion. The sum of areas represent total osteolytic area in each animal.

Summary

VBY-825 showed inhibition of bone lysis in this syngeneic model of murine multiple myeloma. Even though the number of osteoclasts at tumor-bone interface was increased, the total activity of TRACP 5b in serum did not differ from control. These findings suggest that VBY-825 may protect bone from tumor-driven osteolysis and bone matrix destruction. This activity is likely to be mediated primarily through inhibition of cathepsin K, known to be essential in osteolast function, bone remodeling, and resorption.

Conclusions

VBY-825 showed inhibition of bone lysis in this syngeneic model of murine multiple myeloma. Even though the number of osteoclasts at tumor-bone interface was increased, the total activity of TRACP 5b in serum did not differ from control. These findings suggest that VBY-825 may protect bone from tumor-driven osteolysis and bone matrix destruction. This activity is likely to be mediated primarily through inhibition of cathepsin K, known to be essential in osteolast function, bone remodeling, and resorption.

References


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1. www.pharmatest.com