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

JM Tuomela1, MI Suominen2, E Alhoniemi3, KM Fagerlund1, JP Rissanen1, JM Halleen1, LJ Holsinger2.
1Pharmatest Services Ltd, Turku, Finland; 2Viribay Inc., Menlo Park, CA, USA

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 chemo- or radiotherapy, may induce remissions, but MM is generally thought to be incurable, and therefore new treatment options are desperately needed. Proteolytic 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, B, L, S and V.

Aim of the Study

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/KaLwRij mice.

Materials and Methods

5TGM1 cells were inoculated into the tail vein of 7 weeks old female C57BL/KaLwRij 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 (0.5 mg/kg twice a week) which is a FDA approved drug for MM-nd Study group receiving VBY-825 (150 mg/kg daily). Administration of all compounds began one day before tumor cell inoculation and continued until day 34. Disease progression was followed by measuring the levels of paraprotein (IgG), and TRACP 5b in the blood and measuring osteoclast activity in bone radiography and weighing the mice. The mice were sacrificed 5 weeks after inoculation, examined macroscopically, and their bones were collected for histomorphometric analysis.

Conclusions

VBY-825 showed inhibition of bone loss 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 osteoclast function, bone remodeling, and resorption.

Acknowledgements

The study was funded by the Academy of Finland. We thank Johanna Rantanen, Ms Johanna Rantanen, and Ms Johanna Rantanen for their technical assistance.

References

Bortezomib (Velcade®) is an approved anti-myeloma drug with a broad spectrum of antitumoral activity; the development of myeloma bone disease and induced tumor burden in bone in vivo. Oncol Rep 11:1615-1620.

Histomorphometric analysis

Biochemical markers

Radiographic analysis


FIGURE 2. Total tumor burden was measured as secondary and primary tumor burden. a) Total tumor burden and tumor-to-normal bone ratio were determined in bone radiography and weighing the mice. The mice were sacrificed 5 weeks after inoculation, examined macroscopically, and their bones were collected for histomorphometric analysis.

FIGURE 3. A) Trabecular bone area (mm\textsuperscript{2}/median/QU25/4Quartilemax) was determined histomorphometrically. Statistically significant changes were not observed, but there was a trend (p = 0.067) of increased trabecular bone area in the VBY-825 tested group. B) No significant change in the mean osteoclast number at tumor-bone interface (mm\textsuperscript{2}). C) Number of osteoclasts in tumor-bone interface increased in VBY-825 treated groups. D) Representative images of the Masson-Golgi stained histological sections. p = 0.1, * = p < 0.05, NS = Not significant.

FIGURE 4. A) Total osteoclastic area of sacrifice (mm\textsuperscript{2}/median/QU25/4Quartilemax) was determined from K\textsubscript{r} ray radiography. Bortezomib and VBY-825 decreased total osteoclastic area. *p = 0.01. B) Representative K\textsubscript{r} ray images of each treatment group visualizing also the analysis of osteoclast lesions. Each polygon represents one lesion. The sum of areas represent total osteoclastic area in each animal.