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 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. 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 (100 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 (IgG2b) and TRACP 5b in serum, using radiography and weighing the mice. The mice were sacrificed 5 weeks after inoculation, examined macroscopically, and their bones were collected for histomorphometric analysis.

VBY-825 structure

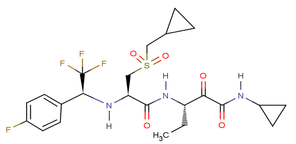

FIGURE 1. The structure of VBY-825, a spectrum-selective cathepsin inhibitor. VBY-825 is potent cathepsin inhibitor with $K_{i(app)}$ values as follows: cathepsin S = 130 pM, cathepsin L = 250 pM, cathepsin B = 330 pM, cathepsin V = 250 pM, cathepsin K = 2.3 nM [Elie et al, (2010) Biochimie 92(11): 1618-24].

Biochemical markers

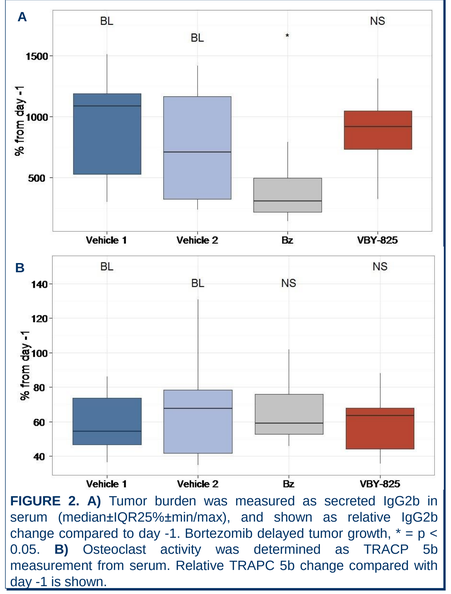

FIGURE 2. A) Tumor burden was measured as secreted IgG2b in serum (median±IQR25%±min/max), and shown as relative IgG2b change compared to day -1. Bortezomib delayed tumor growth, * = p < 0.05. **B)** Osteoclast activity was determined as TRACP 5b measurement from serum. Relative TRAPC 5b change compared with day -1 is shown.

Histomorphometric analysis

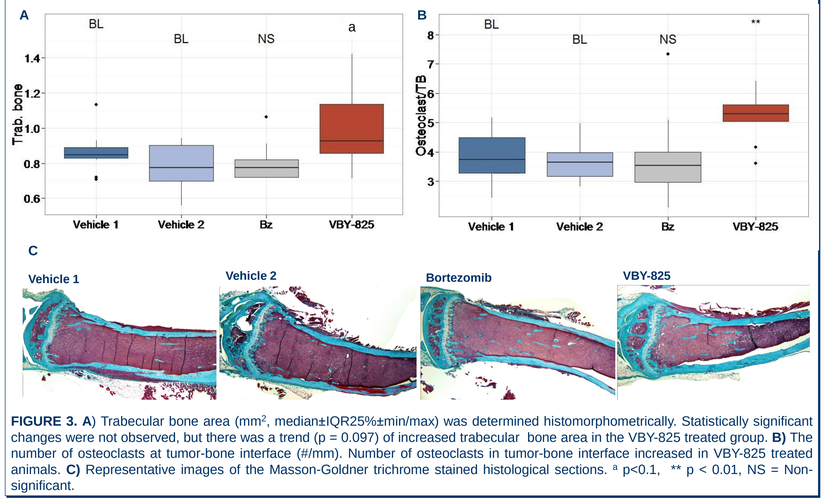

FIGURE 3. A) Trabecular bone area (mm², median±IQR25%±min/max) was determined histomorphometrically. Statistically significant changes were not observed, but there was a trend (p = 0.097) of increased trabecular bone area in the VBY-825 treated group. **B)** The number of osteoclasts at tumor-bone interface (#/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. [a] p<0.1, ** p < 0.01, NS = Non-significant.

Radiographic analysis

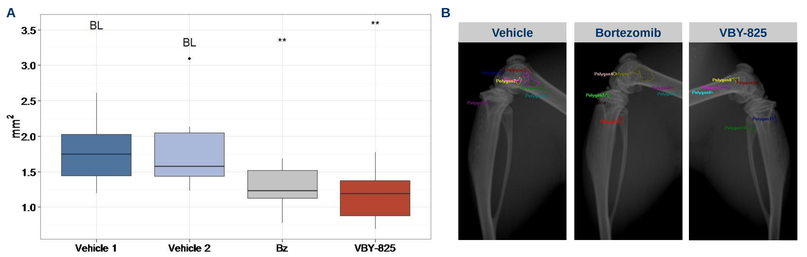

FIGURE 4. A) Total osteolytic area at sacrifice (mm², median±IQR25%±min/max) was determined from X-ray radiography. Bortezomib and VBY-825 decreased total osteolytic area, ** = p < 0.01. **B)** Representative X-ray images of each treatment group visualizing also the analysis of osteolytic lesions. Each polygon represents one lesion. The sum of areas represent total osteolytic area in each animal.

Summary

METHOD / PARAMETER	Bz	VBY-825	METHOD/PARAMETER	Bz	VBY-825
BODY WEIGHT			**HISTOMORPHOMETRY**		
Relative body weight at sacrifice	NS	NS	Relative total bone area	NS	NS
BIOCHEMICAL MARKERS			Relative cortical bone area	NS	NS
Relative IgG2b at sacrifice	*↓	NS	Relative trabecular bone area	NS	[a]↑
Relative TRACP 5b at sacrifice	NS	NS	Relative intraosseous tumor area	NS	NS
RADIOGRAPHY			Total tumor area	NS	NS
Total osteolytic lesion area at sacrifice	**↓	**↓	Osteoclast count	NS	[a]↑
Mean osteolytic lesion area at sacrifice	NS	*↓	Osteoclasts at tumor-bone interface	NS	**↑
Total osteolytic lesion count at sacrifice	*↓	NS			

The comparison against the respective vehicle (vehicle 1 vs. Bz, vehicle 2 vs. VBY-825) ** = p < 0.01, * = p < 0.05, [a] = a trend with p-value < 0.1, NS = Non-significant.

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 osteoclast function, bone remodeling, and resorption.

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References

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