Effects of Cabozantinib in the 5TGM1 murine multiple myeloma model

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Introduction

Cabozantinib, an inhibitor of tyrosine kinases including MET, VEGFR2, and RET, has shown activity in preclinical bone metastasis tumor models (1,3), and clinical activity in patients with castration-resistant prostate cancer and bone metastases (4). Multiple myeloma (MM) is the second most common hematologic malignancy, and represents ~2% of all cancer deaths. MM is a monoclonal B-cell (plasma cell) neoplasia with clinical hallmarks of multiple osteolytic lesions causing bone pain, pathologic fractures, and hypercalcemia. Upregulated HGF and MET are associated with aggressive disease in MM (5), and regulation of plasma cell osteoclastostimulation by the HGF-MET signaling pathway has been implicated in the development of lytic bone disease in these patients (6). Despite availability of active therapies such as bortezomib, lenalidomide, and carfilzomib, MM is generally thought to be incurable, and therefore new treatment options are needed.

Aim of the Study

Our aim was to determine the activity of cabozantinib on bone lesions and tumor burden in the syngeneic 5TGM1 mouse MM model (7).

Materials and Methods

Four experimental groups were included: negative control group receiving vehicle, positive control group receiving bortezomib (6, 25 mg/kg twice a week), low dose cabozantinib group (Cabo 10 mg/kg, PO QD) and high dose cabozantinib group (Cabo 30 mg/kg, PO QD). Seven to eight week old female 5TGM1 mice were allocated to treatment groups (n=15 per group) with equivalent average body weights. On day 0, animals were inoculated with 5TGM1 mouse myeloma cells by IV administration. Dosing began on day 1 and continued daily, until euthanasia on day 28. Body weights were determined twice a week and blood samples were collected on days 1, 15, 22, and 34 for analysis of paraprotein (IgG2b) and lactate-dehydrogenase isoenzyme sLDH (8). The development of osteolytic lesions was detected by radiography at the end of the study (8). Animals were euthanized by IV administration of 100 mg/kg pentobarbital, and measurements were recorded before sacrifice. BM samples were collected at sacrifice for histomorphometric and immunohistochemical analysis. All animal work was approved by the Institutional Animal Care and Use Committee of the University of Turku.

Results

Twelve of 15 mice in the control group were alive at the end of the study (0/15), whereas 11/15 mice in the bortezomib group were alive (8/15), and 12/15 mice survived in both the low and high dose Cabo groups (10/15 and 13/15). Ninety-five percent of the mice survived in the control group, whereas 20% of the mice were alive at the end of the study in the bortezomib group. In the control group, the mean plasma paraprotein level was 4.2±0.3 mg/ml, whereas 0.04±0.01 mg/ml in the bortezomib group. No toxic effects were observed in the high dose Cabo group. A significant increase in tumor burden was observed in the control group (81±10 tumors/mouse) compared to the vehicle group (3±2 tumors/mouse), whereas tumor burden was decreased in both Cabo groups (10±5 tumors/mouse in the low dose Cabo group and 3±2 tumors/mouse in the high dose Cabo group).

Histomorphometric analysis

The average percentage of osteolytic lesions in the control group was 67±7%, whereas 38±5% in the bortezomib group. In the low dose Cabo group, 26±7% of osteolytic lesions were observed, whereas 3±2% in the high dose Cabo group. A significant increase in osteolytic lesion activity was observed in the control group compared to the vehicle group (p<0.001), whereas osteolytic lesion activity was decreased in both Cabo groups (p<0.001). A significant decrease in osteoblast activity was observed in the control group compared to the vehicle group (p<0.001), whereas osteoblast activity was increased in both Cabo groups (p<0.001).

Biochemical markers

The mean serum TRACP 5b level was 153±8 U/L in the control group, whereas 3±2 U/L in the bortezomib group. In the low dose Cabo group, 15±5 U/L were observed, whereas 0±0 U/L in the high dose Cabo group. A significant decrease in TRACP 5b was observed in the control group compared to the vehicle group (p<0.001), whereas TRACP 5b levels were increased in both Cabo groups (p<0.001).

Conclusion

In summary, cabozantinib showed both bone-protective and anti-tumor effects in this murine model of multiple myeloma. Based on these results, further investigation of cabozantinib in multiple myeloma is warranted.

Acknowledgements

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References