TARGETED INHIBITION OF C-MET RECEPTOR BY A SELECTIVE C-MET INHIBITOR, TIVANTINIB, AND A SPECIFIC SHRNA REDUCES BREAST CANCER-DERIVED BONE METASTASES

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ABSTRACT

Breast cancer metastasizes to bone, resulting in debilitating and life-threatening complications associated with significant morbidity and mortality. Because of the clinical significance of this process, there is a need for new strategies aimed at curing the malignant cells in bone metastases or at lessening their effects. A better understanding of the interactions between metastatic breast cancer cells and bone is critical to the development and progression of bone metastases, and thus compounds capable of modulating these interactions could be beneficial in the management of breast cancer bone metastasis. We previously demonstrated the critical role of HGF/c-Met signaling in the in vitro interaction leading to advanced metastases of human breast cancer cells, suggesting the potential utility of the pathway in the development of new drugs aimed at targeting the interaction between metastatic breast cells and bone as a potential mechanism to reduce the development and progression of bone metastases, thus decreasing the clinical complications associated with this pathological process.

MATERIALS AND METHODS

In this work, we investigated the potential therapeutic efficacy of targeting c-Met receptor using both a specific c-Met inhibitor (tivantinib) and RNAi technology in an in vivo bone metastatic model to murine model of breast cancer bone metastasis. Tivantinib is a novel, orally available, small-molecule, multi-domain tyrosine kinase inhibitor (TKI) which was shown to reduce tumor progression and cancer-induced bone destruction with an increase in overall survival.

RESULTS

Chronic administration of tivantinib at the dose of 120 mg/kg delays the development and progression of bone metastatic tumor growth (A) and reduced the formation of bone metastases (B) C. The same dose was ineffective in inhibiting a subcutaneously growing tumor (D).

Reduced bone metastatic tumor burden and tumor-induced osteolysis. The reduced tumor burden was associated with a decreased osteoclast number and activity with an increase in osteoblast activity.

Tivantinib: the chemical structure

shRNA-mediated c-Met silencing further increased Tivantinib efficacy: the combination of tivantinib (120 mg/kg) plus M+ downregulation induced a significant decrease in tumor burden in the bone, reduced bone lesions and increased overall survival of injected mice.

REFERENCES


CONCLUSIONS

These results reveal that c-Met inhibition by tivantinib is effective in delaying the onset and progression of tumor growth in bone and bone-metastatic tumor burden. The results indicate that the systemic administration of tivantinib is not only effective in treating bone metastases, but also reduces bone destruction, possibly decreasing the complications associated with bone metastases. Our results show that the systemic administration of tivantinib induces bone metastases regression, reduction of bone destruction, and an increase in overall survival. The combination of tivantinib and shRNA-mediated c-Met silencing further increased Tivantinib efficacy: the combination of tivantinib (120 mg/kg) plus M+ downregulation induced a significant decrease in tumor burden in the bone, reduced bone lesions and increased overall survival of injected mice.