Newly developed bone targeting platinum complex effectively targets cisplatin resistant relapsed osteosarcoma in a patient-derived orthotopic xenograft (PDOX) mouse model

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INTRODUCTION:
Development of effective therapy is required for refractory osteosarcoma patients. We have developed novel bone targeting platinum compound; 3Pt, and reported its strong inhibitory activity against osteosarcoma cells. Our laboratory pioneered the patient-derived orthotopic xenograft (PDOX) nude mouse model with the technique of surgical orthotopic implantation (SOI). In the present study, bone targeting platinum, 3Pt was evaluated compared to cisplatin on cisplatin resistant relapsed osteosarcoma PDOX mouse model.
METHODS:
A patient with osteosarcoma of distal femur was treated with cisplatin based chemotherapy followed by surgery. Tumor necrosis rate was 70% and the patient developed lung metastasis one year after the surgery. Tumor was resected and was grown orthotopically in the distal femur of mice to establish a patient-derived orthotopic xenograft (PDOX) model. Osteosarcoma cell line was established from the patient original tumor. The novel bone targeting platinum complex, 3Pt was synthesized in pharmacological department of our institution. Cisplatin and 3Pt were used in this study. Osteosarcoma cell survival after a 72 hrs exposure to these compounds was assessed by WST-8 assay, and IC50 value was calculated for each compound. The PDOX models were randomized into the following groups when tumor volume reached around 100 mm^3: G1, control without treatment; G2, cisplatin(CDDP)(6mg/kg, intraperitoneal(i.p.) injection, weekly, for 2 weeks); G3, 3Pt (41.1mg/kg(15μmol/kg), intraperitoneal (i.p.) injection, weekly, for 2 weeks). Tumor size and body weight were measured with calipers and digital balance twice a week.
RESULTS: 3Pt strongly caused concentration-dependent cytocidal effect. IC50 value of 3Pt was significantly low compared to cisplatin. On day 14 after initiation of treatment, 3Pt treatments significantly inhibited tumor growth compared to untreated control: control (G1): 824.6±250.9 mm^3; CDDP (G2): 583.5±169.8 mm^3, 3Pt. (G3): 234.7±75.1 mm^3, (CDDP: $p=0.07$; 3Pt: $p =0.0001$). 3Pt was significantly more effective than CDDP ($p = 0.0003$).
DISCUSSION AND CONCLUSION:
In the present study, we compared a novel bone targeting platinum compound; 3Pt, with CDDP against a CDDP resistant osteosarcoma PDOX nude mouse model. 3Pt showed significantly more efficacy compared to CDDP ($p=0.0003$) which are first-line therapy for this disease. 3Pt is a promising candidate for osteosarcoma since it was effective in a PDOX model.