INTRODUCTION

Prostate cancer is frequently associated with metastasis to bone. The resulting tumors are often osteolytic and lead to the formation of fragile bone, increased chance of fractures and severe bone pain.

Bone metastasis results in significant morbidity and poor prognosis.

Radium-223 dichloride (Ra-223, Xofigo®) is a alpha-emitting radiopharmaceutical that binds to hydroxyapatite in bone and induces DNA double-strand breaks in cancer cells. We evaluated the anti-tumor mode-of-action of Ra-223. In study 1, the animals were stratified into two groups for vehicle and Ra-223 treatment (300 kBq/kg, i.v.). Treatment started 1 week after the last dose of vehicle. The animals were sacrificed 5 weeks after the last treatment, and median values, respectively. In all cases p-values were calculated using t-test, but in (A) logarithmic transformation was performed first (n=11).

MATERIALS AND METHODS

The therapeutic effects of Ra-223 were investigated in a clinically relevant, patient-derived prostate cancer xenograft model. The tumor cells were implanted into the bone marrow cavity. Tumor growth was monitored by performing biweekly intratumoral measurements. The tumor-bearing tibias were excised 5 weeks after the last Ra-223 dosing. The samples (embedded in methyl methacrylate) was used to define osteoblastic and osteoclasts. Autoradiography analysis of β-H2AX molecules using 10 cell diameters (<100 µm), potent radiation effects on the tumor microenvironment are statistically significant (Fig. 5).

CONTROL TIBIA (VEHICLE TREATED)

Figure 1. Ra-223 (300 kBq/kg, i.v.) dramatically reduces bone volume in tumor-bearing tibias and concomitantly increases bone volume in healthy tibias. The bone volume is expressed as bone volume over total volume (BV/TV) and bone volume over bone mineral area (BV/BA). Comparison of the mean values was performed using one-way ANOVA, and pairwise comparisons were performed after vehicle dosing. P-values were calculated using one-way ANOVA test with Kruskal-Wallis test to determine the difference between the groups. (A) Total tissue area (consisting of bone, bone marrow, if any, and soft tissue), and median values, respectively. (B) Tumor-bearing tibias treated with vehicle or Ra-223, respectively. The results were compared using Mantel-Cox log-rank test in the case of tumor-bearing tibias, while the effect was reversed in healthy tibias.

RA-223 TREATED TIBIA

Figure 2. Ra-223 treatment inhibits the number of osteoblasts relative to bone surface (300 kBq/kg, i.v.) in tumor-bearing tibias, while the effect was reversed in healthy tibias. (A) The number of osteoblasts was calculated using 10 cell diameters (<100 µm), and mice with PSA > 5 ng/ml at dosing start. There were less visceral metastases in Ra-223 treated mice, but the difference was not statistically significant (Fig. 5).

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