Prostate Cancer Bone Metastasis Model for Preclinical Evaluation of Radiotherapeutics

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Introduction

Bone metastases cause high mortality in bone metastatic castration-resistant prostate cancer (mCRCP) patients. Several targeted radiolabeled and combination treatments for prostate cancer are in development after approval of radium-223 dichloride (Ra-223 dichloride, Xofigo®) for the treatment of mCRCP.

The aim of the study was to evaluate the growth of LNCAp human prostate cancer cells in bone of NMRI nude mice in order to widen the range of models that can be used to test novel radiotherapeutics. Previously used NOD-SCID mice have a defect in the DNA damage repair system that sensitizes them to radiation and DNA damage repair inhibitors.

Materials and Methods

Male NMRI nude mice (Janvier, France) aged 6-8 weeks were inoculated with 2x10^5 LNCAp cells (ATCC, USA) into the tibia, modeling tumor growth in bone. The mice were randomized to treatment groups based on serum prostate specific antigen (PSA, R&D Systems, USA) levels, and cancer-induced changes in bone (bone lesions) were evaluated by X-ray imaging (Faxitron, USA) at 6 weeks after inoculation of the cancer cells. The mice were treated intravenously with 30 kBq/kg of Ra-223 dichloride (Oak Ridge National Laboratory, USA) or citrate buffer at study weeks 6 and 10. During the study, the tumor growth was followed by serum PSA measurements and tumor-induced bone lesions by X-ray imaging. The bone formation marker serum PINP (IDS Plc, UK) was followed during the study. The study was terminated 12 weeks after inoculation of the cancer cells. Tumor, bone, and fibrotic areas were evaluated by histology.

Efficacy of Ra-223 dichloride

FIGURE 1. A) Serum PSA levels (ng/ml, mean ± SEM) in vehicle and Ra-223 dichloride treated mice. Individual values are presented on the right panel. Ra-223 dichloride decreased serum PSA levels (p<0.0029 ***). B) Serum PINP levels (ng/ml, mean ± SEM). In vehicle and Ra-223 dichloride treated mice. Individual values are presented on the right panel. Ra-223 dichloride decreased serum PINP levels (p<0.0020 ***). C) Bone lesion area (mm², mean ± SEM) in vehicle and Ra-223 dichloride treated mice. Individual values are presented on the right panel. Ra-223 dichloride decreased the bone lesion area (p<0.0194 *). D) Representative X-ray images from vehicle and Ra-223 dichloride treated mice at endpoint.

Histology

FIGURE 2. A) Representative HE stainings from tumor-bearing tibias in vehicle and Ra-223 dichloride treated mice. Magnification 5x. B) Tumor area in the bone marrow (mm², median with IQR). Ra-223 dichloride decreased the tumor area in bone marrow (p<0.0123 *). C) Bone area in the bone marrow (mm², median with IQR). No statistically significant differences were observed (p=0.5655 NS). D) Fibrotic area in the bone marrow (mm², median with IQR). Ra-223 dichloride treatment induced fibrotic changes in the bone marrow (p<0.001 ***). Example image of fibrotic area in bone marrow on the right, magnification 20x. Abbreviations: T = tumor; F = fibrotic area.

Summary

- Ra-223 dichloride was well tolerated in NMRI nude mice
- A tumor take rate of 50% was observed at 6 weeks based on evaluation of serum PSA levels and bone lesions
- LNCAp tumors induced osteoblastic-mixed bone lesions and Ra-223 dichloride reduced the progression of these lesions and decreased serum PSA and PINP levels
- Based on histological evaluation, 60% of Ra-223 dichloride treated mice were tumor free at the end of the study
- Histological evaluation showed increased fibrotic areas and changes in tumor cell morphology in Ra-223 dichloride treated mice

Conclusions

NMRI nude mice can be used in the prostate cancer bone metastasis model utilizing LNCAp cells. Furthermore, Ra-223 dichloride was successfully validated as a standard-of-care reference compound. This model is of high importance when assessing efficacy of different radiotherapeutics as mono- or combination treatments against bone metastases. In the future, models expanding to use humanized mice can be used to evaluate combination therapies also in the field of immuno-oncology.

References


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