Radium-223 dichloride exhibits dual mode-of-action inhibiting both tumor and tumor-induced bone growth in two osteoblastic prostate cancer models

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INTRODUCTION

Prostate cancer is frequently associated with metastasis to bone. Bone tumors are often osteoblastic and lead to the formation of fragile bone, increased chance of fractures, severe bone pain, significant morbidity and poor prognosis. Radium-223 dichloride (Ra-223, Xofigo®), an alpha-emitting radionuclide, binds to hydroxy-apatite in bone and provides targeted radiation therapy against bone metastases1. Ra-223 improves overall survival in prostate cancer patients with bone metastases1 and Xofigo® has been approved for the treatment of castration resistant prostate cancer (CRPC) with symptomatic bone metastases and no known visceral metastatic disease throughout the world2. Ra-223 develops of osteolytic lesions and improves survival in a mouse model of osteolytic breast cancer bone metastasis via a dual mode-of-action on both tumor cells and osteoclasts3.

AIM OF THE STUDY

To investigate the efficacy and mode-of-action of radium-223 dichloride (Ra-223, Xofigo®) in two clinically relevant prostate cancer xenograft models.

MATERIALS AND METHODS

Mouse models and treatments

Ra-223 therapeutic effects were investigated in two clinically relevant prostate cancer xenograft models: 1) LuCaP cell line model (ATCC, European distributor LGC Bayer from the University of Washington; LuCaP 58 (Ra-223) and LuCaP 58 (vehicle)) and 2) LNCaP 58 xenograft model (ATCC, European distributor LGC). Mice were dosed with 300 kBq/kg of Ra-223 and sacrificed 6-9 weeks later. Treatment with vehicle was used as control as indicated in the study design below.

Mouse xenograft models and treatments

Mouse models and treatments

RESULTS


Figure 2. Ra-223 reduces total bone area, relative trabecular bone area and osteoclast numbers in tumor-bearing mice. A) Representative micro-CT images of LNCaP tumors. B) Total bone area of LNCaP tumors. C) Relative trabecular bone area of LNCaP tumors. D) Osteoclast cell number of LNCaP tumors. E) Osteoclast cell surface of LNCaP tumors. F) Osteoclast bone resorption area of LNCaP tumors.

SUMMARY

Radium-223 dichloride inhibits prostate cancer growth in two clinically relevant prostate cancer models. Ra-223 reduces disease progression (micro-CT; Fig. 1A-D), inhibits tumor-induced osteoblastic bone growth and protects normal bone architecture leading to reduced bone volume (Fig. 1E) and tumor mass (Fig. 2A) in two prostate cancer models. Ra-223 suppresses bone metabolic activity as evidenced by decreased number of osteoblasts and osteoclasts (Fig. 2D-E) and reduced level of bone formation marker PINP (Fig. 2F).

Conclusions

1. Ra-223 reduces disease progression (micro-CT; Fig. 1A-D), inhibits tumor-induced osteoblastic bone growth and protects normal bone architecture leading to reduced bone volume (Fig. 1E) and tumor mass (Fig. 2A) in two prostate cancer models. Ra-223 suppresses bone metabolic activity as evidenced by decreased number of osteoblasts and osteoclasts (Fig. 2D-E) and reduced level of bone formation marker PINP (Fig. 2F).

2. Ra-223 treatment results in lower PSA levels (Fig. 3A), suppressed tumor areas (Fig. 3B) and a trend for increased necrotic tumor area (Fig. 3C), indicating constrained tumor growth in metastatic prostate cancer.

3. In the LuCaP 58 model, DNA double-strand breaks are enhanced in cancer cells as early as 24 hours after Ra-223 administration (Fig. 4B) and percentage of necrotic tumor area is slightly increased 48 hours after Ra-223 administration (Fig. 4C) providing further evidence for its dual mode-of-action.

4. The deposition of Ra-223 in the intra-tumor bone matrix and as an artefact range of 2-10 cell diameters (~100 μm) suggests potent radiation effects on the tumor microenvironment.

CONCLUSIONS

1. Ra-223 dichloride (Xofigo®) inhibits disease progression in both the cell-line based LuCaP and the abiraterone-resistant PDX LuCaP prostate cancer models.

2. Ra-223 therapy exhibits a dual mode-of-action that impacts on tumor growth and on tumor-induced bone reactions, both important players in the destructive vicious cycle of osteoblastic bone metastasis in prostate cancer (Fig. 6).

3. Our findings confirm the previously reported beneficial effects of Ra-223 and strongly support further development of Radium-223 for the treatment of patients with prostate cancer.