Radium-223 dichloride (radium-223, Xofigo®) is a targeted alpha therapy which prolongs the survival of castration-resistant prostate cancer (CRPC) patients with symptomatic bone metastases without known visceral metastases.1

As a calcium-mimetic, radium-223 selectively binds to hydroxyapatite and targets areas of high bone turnover such as bone metastases.2

Radium-223 inhibits disease progression by reducing tumor growth and tumor-induced pathological bone reaction in breast and prostate cancer mouse models (Fig. 1).3

The direct cytotoxic effects of radium-223 on local trabecular meshwork (TM) cells and disease-driving osteoblasts and osteoclasts have been established in immunodeficient models.2

The effects of radium-223 on local immune cells are unknown, and these cells may also be involved in the antitumor efficacy of radium-223. However, investigation of the potential immune mode-of-action component of radium-223 reveals successful development of immunocompetent TM models. Furthermore, these models would be needed for the testing of radium-223 in combination with immuno-oncologic drugs.

Here, we report the effects of radium-223 on the development and progression of osteolytic bone lesions and on survival in the syngeneic intratibial MBT-2 murine bladder cancer model in immunocompetent mice.

Methods

Female 5-7-week-old C3H/HeNHsd mice were injected intratibially with 5x10^5 MBT-2 cells on day 0. The mice were stratified based on body weight (less than/less than or equal to group average). The mice were treated on days 10, 18, 25, and 76. The follow-up radiography was performed on days 18, 25, 76, and 158. D(0) was the first mice in the control group met the sacrifice criteria on study day 24.

RESULTS

Radium-223 inhibits cancer growth in bone and tumor-induced bone destruction

Around day 25, when mice with extensive bone lesion were sacrificed, the tumor growth in bone was stabilized in the control group.

Figure 1. Radium-223 therapy exhibits a dual targeting mode-of-action that destroys tumor cells and inhibits tumor-induced pathologic bone reaction. Radium-223 inhibits cancer growth in bone and tumor-induced bone destruction.

Based on X-ray imaging 25 days after cancer cell inoculation, radium-223 treatment reduced the total bone lesion area compared to the control treatment (p<0.001) (Fig. 4).

Radium-223 decreased the tumor-bearing tibia weight compared to the control (p=0.0040) suggesting an inhibitory effect on tumor growth (Fig. 5).

The first mice in the control group met the sacrifice criteria on study day 24 (Fig. 6).

Survival was 97% in the radium-223 treatment group compared to 65% in the control group (p=0.001) on day 40 (Fig. 6).

The survival curves plateaued at 52% after 84 days in the control group and 68% after 112 days in the radium-223 treatment group. The study was terminated on day 158.

At the end of the study, the difference in survival between the control and the radium-223 treatment group was not statistically significant.

CONCLUSIONS

Radium-223 inhibits cancer growth in bone and ameliorates tumor-induced bone destruction resulting in a beneficial effect on survival in the intratibial MBT-2 murine bladder cancer model of osteolytic bone metastasis.

The single agent in vivo efficacy of radium-223 results in a moderate beneficial effect on survival.

The promising results obtained in this immune-competent mouse model warrant further investigation of radium-223 in combination with immuno-oncologic treatments such as checkpoint inhibitors.

REFERENCES


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