Radium-223 Chloride Completely Prevents Tumor Growth in Bone and Increases Survival in a Mouse Model of Breast Cancer Bone Metastases in Preventive and micro-metastatic Settings

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INTRODUCTION

• Radium-223 chloride (Alpharadin; Bayer HealthCare/Algeta ASA, Oslo, Norway) is an alpha-pharmaceutical shown to improve overall survival in ALSYMPCA, a phase III clinical study (Alpharadin in SYMptomatic Prostate Cancer) for the treatment of castration-resistant prostate cancer with bone metastases.
• Radium-223 is a calcium mimetic alpha-pharmaceutical that localizes to bone, where the emission of alpha-particles provides an efficient and localized radiation treatment to metastatic skeletal tumor lesions.
• Radium-223 increased symptomatic survival in a preclinical model of osteolytic breast cancer bone metastases in nude rats.
• Radium-223 decreased osteolyis and tumor burden in a preclinical model of established breast cancer bone metastases in nude mice.
• This study aimed to clarify the effects of radium-223 on the development of breast cancer bone metastases when administered in the preventive and micro-metastatic settings.

MATERIALS AND METHODS

• The in vivo effects were studied using a model where human MDA-MB-231(SA)-green fluorescent protein (GFP) cells (a generous gift from Professor Theresa Guise, University of Indiana) were inoculated into nude mice via left cardiac ventricle. Two separate studies, a bone metastasis study and a survival study, were performed.

• In the bone metastasis study, the animals were randomized to four groups (n=12) based on body weights. Animals were dosed with either vehicle or a single dose of radium-223 (300 kBq/kg) at day -1 (preventive setting), day 2 (micro-metastatic setting), or day 15 (a separate treatment arm of the study). Additionally, three extra vehicle-treated mice were sacrificed at day 2 for immunohistochemical (pancytokeratin and GFP) detection of tumor cells in the bone marrow. Radiography and fluorescence imaging were performed at sacrifice (day 25). Tumor burden was analyzed from mid-sagittal sections of both hind limbs. Histomorphometric analysis was performed from Meso-Goldner trichrome- and TRAP-stained mid-sagittal sections of both hind limbs.
• In the survival study, the animals were randomized to three groups (n=12) based on body weights. The animals were dosed with either vehicle or a single dose of radium-223 (300 kBq/kg) at day -1 or 2. Radiography and fluorescence imaging were performed on animals surviving to day 50.
• Statistical analysis was performed using one-way ANOVA followed by Dunnett’s test for comparison against the control group and Student’s t-test for comparison and tumor burden and the amount of bone in the hind limbs of animals.

RESULTS

• Radium-223 deposition localized to bone, where the emission of alpha-particles provides an efficient and localized radiation treatment to metastatic skeletal tumor lesions.
• Radium-223 administered at day -1 or 2 prevented cachexia when administered at days -1, 2, or 15, respectively, and only two groups became paraplegic, weight loss was over 30% when administered at days -1 and 2.
• Radium-223 administered in a preventive or day -1, 2 and 15 treatment setting completely prevented dissemination of tumor cells in bone marrow.
• Tumor burden and the amount of bone in the hind limbs of animals was analyzed from mid-sagittal sections of both hind limbs.
• These findings strongly support the clinical development of radium-223 for patients at risk of developing bone metastases.

CONCLUSIONS

• Radium-223 is an alpha-pharmaceutical shown to improve overall survival by 2.8 months (HR=0.695; 95% CI, 0.552-0.875; two-sided p=0.00185) in the phase III ALSYMPCA study in the treatment of castration-resistant prostate cancer with bone metastases.
• Radium-223 administered in a preventive or micro-metastatic setting completely prevented establishment of breast cancer bone metastases and increased survival in this preclinical model.
• These findings strongly support the clinical development of radium-223 for patients at risk of developing bone metastases.

Table 1. The effects of radium-223 on cachexia

<table>
<thead>
<tr>
<th>Vehicle control</th>
<th>Radium-223 at day -1</th>
<th>Radium-223 at day 2</th>
<th>Radium-223 at day 15</th>
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</thead>
<tbody>
<tr>
<td>Cachexia (%)</td>
<td>6.7</td>
<td>0.0</td>
<td>0.0</td>
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<tr>
<td>P value</td>
<td>0.005**</td>
<td>0.005**</td>
<td>0.559</td>
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REFERENCES