Letters

OBSERVATION

Alpha Emitter Radium 223 in High-Risk Osteosarcoma: First Clinical Evidence of Response and Blood-Brain Barrier Penetration

Osteosarcoma is the most common primary malignant condition of the bone in children, adolescents, and young adults. We have reached a therapeutic plateau with standard chemotherapy. Patients with relapsed disease have a dismal prognosis. There have been no new therapies for osteosarcoma approved by the US Food and Drug Administration (FDA) in the last 3 decades.

Radium 223 dichloride (223RaCl2) is an alpha-emitting radiopharmaceutical and calcimimetic that has intrinsic bone-targeting properties. It recently received FDA approval for prostate cancer with bone metastases. Preclinical studies in mice with human osteosarcoma xenografts and in dogs with osteosarcoma have shown that 223RaCl2 is a potentially low-toxicity, high-efficacy targeted agent for osteosarcoma, which is an osteoblastic bone-forming tumor. Knowing this, we hypothesized that 223RaCl2 could be safely administered to patients with osteosarcoma and that early response or resistance signals could be assessed by quantitative or qualitative correlative imaging studies.

We designed a phase 1 clinical trial for patients with progressive, locally recurrent, or metastatic osteosarcoma with no standard curative options available with at least one indicator lesion avid on technetium Tc 99m-methylene diphosphonate scan. The protocol was approved by the University of Texas MD Anderson Cancer Center institutional review board, and all participants provided written informed consent. The trial is ongoing and registered (NCT01833520).

Report of a Case | A man in his 20s with lung and brain metastatic osteosarcoma had been initially diagnosed with left femur osteosarcoma and had undergone standard osteosarcoma chemotherapy, surgery, and rotationplasty. A pathologic analysis showed less than 90% necrosis. He received preadjuvant and adjuvant high-dose methotrexate, cisplatin + doxorubicin, and ifosfamide + etoposide. While on surveillance, he developed sudden left hip pain and chest pain. Imaging revealed recurrence in the left ischium, a large calcific right lung mass, and cerebellar metastases. Biopsy confirmed osteosarcoma.

The patient was enrolled in the 223RaCl2 osteosarcoma clinical trial. Baseline imaging studies were performed, including a positron emission tomography–computed tomography (PET-CT) bone scan using fluoride 18 (18F) (Na18F-PET–CT) and brain magnetic resonance imaging (MRI). Serum markers of bone turnover were also obtained. The patient received 3 infusions of 223RaCl2, 75 kBq/kg, at 4-week intervals, with a total administered dose of 14.44 MBq (0.390 mCi). Posttreatment imaging showed positive response to therapy at most sites (Table), including the dominant left cerebellar metastasis. On MRI, the cerebellar lesion decreased from 1.5 cm at baseline to 1.2 cm after treatment, with resolution of perilesional edema (Figure). On Na18F-PET–CT, the cerebellar metastasis decreased significantly in intensity following radium therapy (Figure). However, both MRI and Na18F-PET–CT showed interval development of new cerebellar metastases smaller than 5 mm, and the patient was disenrolled from the clinical trial because of progressive disease. Patient reported a clinical reduction in bone pain after 3 doses of 223RaCl2 and had no grade 3 or 4 toxic effects related to 223RaCl2.

Discussion | This is the first clinical evidence of an alpha particle with blood-brain barrier (BBB) penetration and early evidence of 223RaCl2 activity in osteosarcoma. Interestingly, review of the literature revealed BBB penetration of a beta particle, Yttrium Y 90 (90Y) ibritumomab tiuxetan, given intravenously to a patient with primary central nervous system lymphoma. After 90Y ibritumomab tiuxetan administration, there was complete response in enhancing tumor where the BBB was leaky, but lesions occurred in other brain regions, where the BBB was intact.

Once a radionuclide is deposited in or near a cancer cell, the rate (half-life), range, and energy of radioactive particle emissions (MeV) are quite different within the target zone for alpha vs beta emitters. The charged alpha particles from 223Ra have far more mass and energy than beta particles (electrons). In the present patient, both imaging and biomarkers showed a definite 223RaCl2 response signal. A dose-escalation study is underway to further define the role of single-agent 223RaCl2 in osteosarcoma. An adjuvant trial with combined chemotherapy–targeted therapy and 223RaCl2 is warranted.

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Table. Reductions in PET-CT Metabolic Activity From Baseline to 3 Months of Treatment

<table>
<thead>
<tr>
<th>Scan Type</th>
<th>Baseline</th>
<th>3 Months</th>
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<tbody>
<tr>
<td>FDG–PET–CT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SUVmax</td>
<td>11.70</td>
<td>9.00</td>
</tr>
<tr>
<td>TLG</td>
<td>1382.17</td>
<td>1159.76</td>
</tr>
<tr>
<td>Na18F–PET–CT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SUVmax</td>
<td>56.58</td>
<td>39.25</td>
</tr>
<tr>
<td>TF10</td>
<td>5342.75</td>
<td>3740.28</td>
</tr>
</tbody>
</table>

Abbreviations: FDG, fluordeoxyglucose; Na18F, sodium fluoride 18; PET–CT, positron emission tomography–computed tomography; SUV max, maximum standardized uptake value; TF10, total Na18F activity in all malignant lesions with SUV of 10 or greater (an estimate of total metastatic burden); TLG, total lesion glycolysis.
A and B, An axial positron emission tomography–computed tomography (PET-CT) bone scan using fluoride 18 (18F) (Na18F-PET–CT) (A) and T1 postcontrast magnetic resonance image (MRI) (B) show a metastatic lesion in the left cerebellar hemisphere (blue arrowheads). C, After 3 infusions of 223RaCl2, Na18F-PET–CT shows that the intensity of uptake in the left cerebellar metastasis has decreased significantly, with a decline in metabolic activity standardized uptake value from 42.3 to 12.7 (−70%) (blue arrowhead). D, Posttreatment MRI shows corresponding decrease in gadolinium contrast enhancement and resolution of edema (blue arrowhead). C and D, Both Na18F-PET–CT and MRI posttreatment images show new cerebellar metastases such as that shown in the right cerebellum (yellow arrowheads). E-H, In support of the imaging findings of positive response, the noted serum markers of bone turnover decreased following initiation of treatment with 223RaCl2.

**Figure. Pretherapy and Posttherapy Images and Supporting Charts Show:**

**Signals of Activity of Radium 223 Dichloride (223RaCl2) in Osteosarcoma**

**Letters**

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