Alpharadin, a novel, targeted approach for treatment of bone metastases from CRPC – calculated alpha-particle dosimetry compared to a favourable clinical safety profile

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BACKGROUND

Alpharadin (radium-223 dichloride) is the first-in-class alpha-pharmaceutical which has a potent and highly targeted antitumour effect on bone metastases* and a highly tolerable side effect profile*. Bone-targeted Alpharadin emits alpha-particles with an ultra-short range of 2-10 cell diameters, generating highly localized and intense radiation zones. The high-energy alpha-particle radiation induces lethal double-stranded DNA breaks resulting in a potent and highly localized cytotoxic effect in the target areas containing metastatic cancer cells. The short path length of the alpha particles also ensures that toxicity to adjacent healthy tissue and particularly the bone marrow is kept to a minimum in Phase I trials. Alpharadin showed a statistically significant improvement in overall survival compared to placebo2,4, and a consistent improvement in disease-related biomarkers3 and pain1.

The aim of the present study was to investigate the biodistribution and dosimetry of the agent.

METHODS AND STUDY DESIGN

Six patients with bone metastases from CRPC received two Alpharadin injections of 100kBq/kg (0.007 nCi/kg) 6 weeks apart. Activity in blood (white blood and plasma) samples was measured before and at regular intervals after injection. A complete collection of urine and feces was performed for 48 hours following Alpharadin administration. Whole body retention was assessed by a sodium iodide (NaI) detector. Biodistribution of radium-223 was assessed by planar whole body scintillation gamma camera imaging. Radiation dose was calculated using CLINARA/EXD3 with adjustments in the alpha-particle contribution to the dose for selected source-target organ combinations. Specifically, the absorbed dose to the relevant target cells in the gastrointestinal (GI) tract from emissions in the contents was reduced to reflect the short range of the alpha particles as well as the observation that transport of Alpharadin is almost exclusively through the small intestine wall. Doses from activity in the red marrow and osteogenic fractions that were specifically calculated for alpha-particles and that better account for the detailed geometry and cellularity of the marrow trabecular bone matrix.

The calculated radiation doses were correlated with clinical safety, as assessed across phase I and II studies (N = 202) (see Figure 2).

REFERENCES


RESULTS

Figure 2: Study design

Figure 3: Activity concentration in whole blood as a function of time for all patients (both injections)

More than 75% of the activity had left the blood and plasma at 15 minutes after injection. Only 4% ± 1% (range 2-6%) of the activity remained in the blood at 4 hours post injection, decreasing to less than 1% at 72 hours. Radionuclide selectively targeted bone tissue and was localized in areas of increased bone formation in bone metastases. The remainder was rapidly eliminated predominantly via the GI tract. No specific renal, urinary bladder, cardiac, gut, head or other uptake was visible on scintillation camera images. The activity concentration in the urine was markedly low, resulting in low renal and bladder absorbed doses. The distribution pattern as seen on whole body scintillation gamma camera images is shown in Figure 4.

Figure 4: Baseline anterior 99mTc-scan and anterior whole body scintillation gamma camera images after injection of Alpharadin of a representative patient (images from 2 of 5 scans presented)

With the adjustments described above, the revised calculated mean absorbed doses to organs of interest are presented in Table 1.

Table 1: Calculated absorbed doses to organs of interest

<table>
<thead>
<tr>
<th>Organ</th>
<th>Lowest absorbed dose (Gy/MBq)</th>
<th>Highest absorbed dose (Gy/MBq)</th>
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</thead>
<tbody>
<tr>
<td>Lower large intestinal wall</td>
<td>4.65E-02</td>
<td>1.72E+02</td>
</tr>
<tr>
<td>Small intestine</td>
<td>7.32E-03</td>
<td>2.95E+01</td>
</tr>
<tr>
<td>Upper large intestine wall</td>
<td>3.22E-02</td>
<td>1.20E+02</td>
</tr>
<tr>
<td>Kidneys</td>
<td>3.03E-02</td>
<td>1.19E+02</td>
</tr>
<tr>
<td>Liver</td>
<td>2.97E-03</td>
<td>1.10E+01</td>
</tr>
<tr>
<td>Red marrow</td>
<td>1.30E-01</td>
<td>5.14E+02</td>
</tr>
<tr>
<td>Osteogenic cells</td>
<td>1.15E+00</td>
<td>4.28E+03</td>
</tr>
<tr>
<td>Urinary bladder wall</td>
<td>4.02E-03</td>
<td>1.49E+01</td>
</tr>
</tbody>
</table>

Safety analyses across all Phase I and II studies show that <1% of 292 patients experienced NCI CTG Grade 4 haematological adverse events during the study period. 4% of the patients experienced NCI CTG Grade 3 toxicity for hemoglobin, and <2% experienced NCI CTG Grade 3 for platelets, neutrophils or white blood cells. 20-30% of the patients reported mild to moderate reversible gastrointestinal events such as nausea, vomiting, diarrhoea, constipation. The dosimetry results represent the best possible approximations given current understanding of alpha-particle radiobiology, in vivo, and our inability to measure and model the microdistribution of the alpha emitter in bone and bone marrow. We therefore conclude that the safety of such short-range, high-potency emitters is best determined from clinical observations.

CONCLUSIONS

• Alpharadin is rapidly taken up by bone metastases and excreted through the GI tract.
• Due to the very short range (<100 µm) of alpha particles, only a small volume of red marrow and the intestines receives a significant absorbed radiation dose. This may account for the documented favourable safety profile of Alpharadin in Phase I and II studies.