Radioisotopes reborn: radium–223 and its role in the management of prostate cancer

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Bone metastases are strongly associated with mortality, morbidity, impaired quality of life and increased costs, thus providing a rationale for use of bone-targeted agents for these patients. Bone-seeking radionuclides can specifically target osteoblastic lesions to offer palliation of pain. To take advantage of tumour targeting, relatively short path lengths are desirable. Therefore, radioisotopes emitting alpha particles or beta particles are preferred to those emitting gamma rays. The path of beta emissions can range from 1 to 10mm, whereas alpha particles have a very short path length. Initial clinical studies with bone-seeking compounds were conducted using the beta emitters strontium-89 and samarium-153, which have since been proven to be useful for pain palliation. These agents have Level 1 evidence for pain-control benefits when used alone or in combination with external beam radiotherapy in painful prostatic bone metastases. However, beta emitters have a limited radiobiological effectiveness and are associated with substantial myelotoxicity. Indeed, the toxicity associated with beta emitters limits the dosage that can be given and the use of repeated treatments. In addition, beta emitters have not demonstrated any survival benefit to date. Therefore, beta emitters are only indicated for the treatment of pain associated with bone metastases.

RADIUM–223

Radium-223 (Ra-223; Xofigo), formerly known as alpharadin, is an alpha-emitting radioisotope that delivers high-energy irradiation over a short range, and therefore gives lower penetration into surrounding tissue than beta-emitting compounds, such as samarium-153 and strontium-89. Ra-223 is preferentially absorbed by bone due to its chemical similarity to calcium, and any Ra-223 not taken up by the bone metastases is rapidly cleared to the gut and excreted. While many bone-targeted radioisotopes have an established role for pain management in metastatic prostate cancer, such as strontium and samarium, Ra-223 is the first compound to demonstrate significant overall survival (OS) benefit. In the recently reported phase III ALSYMPCA trial, in men with symptomatic bone-metastatic, castration-resistant prostate
cancers, who had received or were ineligible for docetaxel chemotherapy, Ra-223 treatment resulted in improved OS and delayed skeletally-related events.9

**THE ALSYMPCA TRIAL**

ALSYMPCA evaluated the efficacy and safety of Ra-223 in patients with castration-resistant prostate cancer (CRPC) and skeletal metastases.9 The primary endpoint was OS. The patients were required to have confirmed symptomatic metastatic CRPC, at least ≥2 bone metastases, no visceral metastases and be post-docetaxel or unfit/unwilling for docetaxel. Patients had a PSA of >5ng/ml and none had received chemotherapy in the four weeks prior to enrolment. Patients were stratified by baseline alkaline phosphatase (ALP), bisphosphonate use and prior docetaxel exposure. In the updated analysis, the median survival was longer among patients who received Ra-223 than among those who received placebo by 3.6 months (p<0.001).9 The effect of Ra-223 on OS was consistent across all subgroups (ie regardless of whether they had previously received docetaxel or were currently being treated with bisphosphonates). Ra-223 significantly delayed time to first symptomatic skeletal event versus placebo by a median increase of 5.8 months (p<0.001). Median time to initial opioid use was 6.9 months in the placebo group, but had not yet been reached for men treated with Ra-223. Ra-223 also significantly prolonged the median time to ALP progression (7.4 versus 3.8 months; HR=0.17; 95% CI 0.13–0.22; p<0.001) and median time to PSA progression (2.4 versus 2.1 months; HR=0.64; 95% CI 0.55–0.75; p<0.001).10 Ra-223 was associated with low myelosuppression rates and fewer adverse events.9

**INTRODUCING RA-223 IN THE CLINIC**

Ra-223 treatment is administered as a simple intravenous infusion. It is given as six injections, one every four weeks. It is available in 10ml vials containing 6ml solution and has a half-life of 11.4 days. Ra-223 is administered on an outpatient basis, similar to chemotherapy. However, unlike chemotherapy, it requires additional safety measures such as radiation protection, consideration of legal requirements and forging of new collaborations across departments. Starting a new Ra-223 service requires regulatory licences; radiopharmacy facilities for storage and dispensation; clinical teams to deliver the service; establishment of patient pathways and care plans; funding; and training of personnel (administration and safety training).

Doses of Ra-223 can be measured using standard dose calibrators/probes. In addition, no special radiation precautions are needed as Ra-223 decays to stable lead without long-lived radioactive decay products. Ra-223 can be introduced in any centre that fulfils one or more of the following criteria:

- participated in the ALSYMPCA study
- already uses bone-seeking radionuclides
- already has a nuclear medicine department (probably only for diagnostic purposes).

There are many different models for local delivery involving multidisciplinary teams (oncologists, radiographers, nuclear medicine specialists and supporting staff including nurses, administrative support and oncology services). Collaboration between these disciplines allows for establishment of an optimal Ra-223 service. Figure 1 shows where Ra-223 may fit into the current treatment paradigm for CRPC.

**Patient counselling and education is also an important consideration for patients receiving Ra-223. Some key points to consider are shown in Box 1.**

**CONCLUSION**

The OS benefit and low toxicity with Ra-223 make it an effective, well-tolerated and novel treatment option for advanced prostate cancer.
treatment option for symptomatic bone metastases in patients with prostate cancer. In the ALSYMPCA phase III clinical trial, Ra-223 improved patient survival by 30%. The key challenges concern the practicalities of administering this radioisotope in clinical practice to ensure that appropriate patients can benefit.

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**REFERENCES**

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**Box 1. Advice and considerations for patients taking radium–223 (Ra-223)**

- The patient will be home on the same day
- No contact restrictions: post-procedure there are no restrictions for patients on interaction with others (eg family, caregivers)
- Patients should maintain good hygiene practices following administration, as radioactivity will be present in excreted body waste for at least four weeks after the last injection
- Ra-223 is excreted via the intestinal system and can cause mild diarrhoea, therefore patients should ensure that they are adequately hydrated