Novel treatment (new drug/intervention; established drug/procedure in new situation)

Clinical benefits of alpharadin in castrate-chemotherapy-resistant prostate cancer: case report and literature review

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Summary

Prostate cancer has the second-highest mortality worldwide in men. The most common site of metastasis is bone. Bone metastases and their resulting complications represent a significant source of morbidity. Radioisotopes have been used for treatment of painful bony metastases. Although shown to decrease pain and analgesia use, this has not improved outcomes. The following case report describes a patient with castrate-resistant prostate cancer who was treated with the radioisotope radium-223 as part of the phase III clinical trial Alpharadin in Patients with Symptomatic Hormone Refractory Prostate Cancer with Skeletal Metastases (ALSYMPCA). He responded to radium-223 with pain relief, bone scan response, stabilisation of prostate specific antigen (PSA) and normalisation of alkaline phosphatase. Interim analysis of this trial has shown that radium-223 significantly prolongs overall survival, time to first skeletal-related event and is well tolerated. Alpharadin is a new treatment option for men with castrate-resistant prostate cancer and symptomatic bone metastases.

BACKGROUND

Prostate cancer is the most common cancer in men and has the second-highest mortality worldwide.¹ The most common site of metastasis for prostate cancer is bone. Bone metastases and the resultant complications represent a significant source of morbidity for these patients. Radioisotopes such as strontium-89 (Sr-89) and samarium-153 (Sm-153) have been used in the past for treatment of painful bony metastases. Although they have been shown to decrease pain and analgesia use, this has not translated into improved survival. The following case report describes a patient with castrate-resistant prostate cancer who was treated with the radioisotope radium-223 (alpharadin) as part of the phase III clinical trial of Alpharadin in Patients with Symptomatic Hormone Refractory Prostate Cancer with Skeletal Metastases (ALSYMPCA). The patient had prior treatment with docetaxel-based chemotherapy for metastatic disease. He responded to radium-223 with subjective pain relief, bone scan response, stabilisation of prostate specific antigen (PSA) and normalisation of alkaline phosphatase (ALP). Interim analysis of this trial has shown that radium-223 significantly prolongs overall survival and time to first skeletal-related event (SRE) and is well tolerated.² Alpharadin is a new treatment option for men with castrate-resistant prostate cancer and symptomatic bone metastases.

CASE PRESENTATION

Our patient was initially diagnosed with a clinical T2b, Gleason 8 and PSA 18 adenocarcinoma of that prostate.

INVESTIGATIONS

Initial staging showed no evidence of metastatic disease.

TREATMENT

He was treated with radical radiotherapy and adjuvant LHRH agonist therapy. The patient received 4600 cGy in 23 fractions to the prostate, seminal vesicles and first echelon lymph nodes followed by a boost of 3000 cGy in 15 fractions to the prostate alone. Neoadjuvant, concurrent and adjuvant hormonal ablation was carried out with goserelin acetate injections every 3 months for a total of 5 years.

His PSA nadired at 0.02. Several months following, the patient developed a PSA relapse. Restaging at that time showed no evidence of metastatic disease. Bicalutamide was added to LHRH therapy without evidence of a PSA response. Alternative hormonal manipulations including flutamide and ketoconazole were not successful. Oral antiandrogen therapy was discontinued and the patient remained on single agent LHRH therapy.

At 6 years postinitial treatment follow-up CT scan demonstrated small volume nodal metastases in the para-aortic and pelvic regions and bone scan showed multiple bone metastases. At this time the patient was referred to medical oncology. He was treated with monthly zoledronic acid and enrolled in the taxotere/prednisone and dasatinib phase III trial (NCT00744497). He had a PSA and radiographic clinical response but chemotherapy was discontinued after two cycles because of grade 3 mucositis. He demonstrated further disease progression and eventually the patient elected for rechallenge with taxotere (off study). After three cycles chemotherapy was discontinued due to lack of therapeutic benefit.

He remained symptomatic from bone metastases and as a result was considered for the alpharadin clinical trial (NCT00699751). At study entry his bone scan demonstrated widespread metastases to the axial and proximal appendicular skeleton (figure 1A), a PSA of 994 with a

Figure 1 : Bone scan of our patient (A) prior to entry on the alpharadin clinical trial (February 2010) and (B) after restaging following treatment (January 2011).

PSA doubling time of 4 months. He was requiring hydromorphone contin 15 mg twice daily with breakthrough hydromorphone for bone pain. The patient received six cycles of 50 kBq/kg administered intravenously every 4 weeks for 4 months, in accordance to the double-blinded placebo-controlled protocol.

OUTCOME AND FOLLOW-UP

Alpharadin provided subjective clinical benefit to the patient with improvement of his pain and he was able to discontinue the narcotics within 6 weeks of start of therapy. His duration of complete pain relief was 4 months subsequent to the completion of therapy. During the first 4 months of treatment the patient had no SREs. Follow-up bone scan showed a significant reduction in activity of all skeletal metastases except for the right humerus (Figure 1B). There was concordant normalisation of ALP and stabilisation of PSA. Alpharadin therapy was well tolerated with no nausea, diarrhoea, systemic reaction or pain flare. He did have some treated-related cytopenias and required two blood transfusions for anaemia-related fatigue.

On last follow-up the patient's PSA was rising and imaging revealed progression of bone metastases while receiving abiraterone acetate. At this time abiraterone was discontinued and the patient was discharged to a palliative care hospital for supportive care and has since passed away.

DISCUSSION

Prostate cancer is the most common cancer in men and has the second-highest mortality worldwide.¹ The most common site of metastasis for prostate cancer is bone. Prostate cancer and the use of androgen deprivation therapies are risk factors for bone loss in men and consequently lead to increased risk of bone pain, SREs and poor quality of life.^{3–8} Bone pain is a significant cause of morbidity in patients with metastatic prostate cancer. The median survival of castrate-resistant prostate cancer is only 1–2 years.^{9 10}

This case report highlights a patient with metastatic castrate-resistant prostate cancer who was refractory to hormone manipulation, intolerant to chemotherapy and benefited from treatment with radium-223. Benefits were both subjective (clinically meaningful pain relief) and objective (bone scan improvement, stabilisation of PSA and normalisation of the bone turnover enzyme ALP).

Bisphosphonates inhibit osteoclast-mediated bone resorption and have been found to delay SREs in various malignancies (breast/prostate cancer and multiple myeloma). Zoledronic acid has been shown to decrease SREs by 36% in prostate cancer patients with bone metastasis compared to placebo.¹¹ In malignancy, bone destruction and fragility result from excess osteoclastic activity. RANK ligand plays a major role in osteoclast formation and survival. Denosumab is a human monoclonal antibody with high affinity and specificity for RANK ligand and therefore inhibits osteoclast-mediated bone destruction. In non-metastatic prostate cancer patients receiving the androgen deprivation therapy, denosumab increases bone mineral density at all sites and reduces the incidence of new vertebral fractures.¹² It was also found to be superior to zoledronic acid in preventing SREs in men with castrate-resistant prostate cancer (time to first SRE 20.7 versus 17.1 months, HR 0.82 and $p=0.008$ for superiority).¹³ Although zoledronic acid and denosumab have been shown to decrease SREs in men with metastatic prostate cancer, there have been no improvements in overall survival.

Radioisotopes, such as Sr-89 and Sm-153, localise to and deliver radiation to metastatic bony sites with high specificity and relative sparing of normal bone. This 'bone seeking' feature leads to the delivery of β -radiation to sites of metastatic disease. The main advantages include relative ease of administration (intravenously), ability to treat multiple metastatic sites simultaneously and potential-enhanced therapeutic effect when combined with treatments such as chemotherapy and external beam radiotherapy. A systematic review looking at the role of radiopharmaceuticals in the palliation of painful bone metastasis found that radiopharmaceuticals are associated with improved pain control and decreased use of analgesia.¹⁴ There does not appear to be any significant difference in the efficacy of various radiopharmaceuticals. β -Emitter radioisotopes do not appear to impact overall survival as the original clinical trials were not designed to detect changes in overall survival. Furthermore, it was felt that based on the available evidence β -emitter radiopharmaceuticals should be used in patients with multiple bony metastases when pain control from conventional methods is inadequate. The main toxicity from these agents is mild-to-moderate transient bone marrow suppression.

Alpharadin (radium-223 chloride) is an α -emitting radiopharmaceutical. Radium-223 acts as a 'calcium

mimic' that targets new bone growth in and around bone metastases and this has bone seeking properties similar to other radioisotopes used for bone pain palliation. However, unlike currently used β -emitter radioisotopes, α -particle emissions from radium-223 have a higher linear energy transfer and a range of less than 100 μ m. Therefore, it is able to deliver radiation to a more localised volume and reduce the amount of radiation to adjacent normal structures. In a phase II study, alpharadin was shown to significantly improve ALP and delay time to PSA progression compared to placebo. Median overall survival at 2 years was also improved. Additionally, alpharadin was felt to have a favourable safety profile.¹⁵ These results led to a definitive phase III study which compared alpharadin versus best standard of care in men with symptomatic castrate-resistant prostate cancer (chemotherapy/taxane resistant or patients not eligible for chemotherapy). The inclusion criteria consisted of men with confirmed symptomatic castrate-resistant prostate cancer, >2 bone metastases, no known visceral metastases who were postdocetaxel or unfit for docetaxel. The primary endpoint of this study was overall survival. Secondary endpoints included time to first SRE, ALP normalisation, time to PSA progression, safety and quality of life.

A preplanned interim analysis showed that treatment with radium-223 significantly improved overall survival by 4.5 months at 24-month follow-up (14.0 versus 11.2 months, HR 0.695 and $p=0.00185$). This improvement in overall survival met the predetermined boundary for stopping the clinical trial. Time to first SRE was also significantly improved (13.6 versus 8.4 months, HR 0.610 and $p=0.00046$). ALP normalisation was also associated with a significant improvement in overall survival. Alpharadin also demonstrated a well-tolerated safety profile. Hematological events occurred in 39% of patients treated with alpharadin compared to 34% of patients treated with placebo and were primarily anaemia.²

Alpharadin is the first radioisotope to demonstrate a survival advantage. Our case report illustrates a patient with clinical benefit following alpharadin. Alpharadin is a new exciting treatment option for men with hormone-resistant prostate cancer with symptomatic bone metastases.

Learning points

- ▶ Bone metastases from prostate cancer cause significant morbidity to patients.
- ▶ Patients with castrate-resistant prostate cancer and bone metastasis treated with radium-223 have improved overall survival and time to first skeletal-related event.
- ▶ Radium-223 is well tolerated.
- ▶ Radium-223 is a new treatment option for men with castrate-resistant prostate cancer and symptomatic bone metastases.

Competing interests None.

Patient consent Obtained.

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