NAVIGATING THE mCRPC LANDSCAPE: EXPLORING KEY CLINICAL DECISION POINTS

Summary of presentations from the Bayer-supported satellite symposium, held at the European Association of Urology (EAU) Congress, Madrid, Spain on 22nd March 2015

Chairperson

Fred Saad[1]

Speakers

Gero Kramer,[2] Bertrand Tombal,[3] Jürgen Gschwend[4]

1. University of Montreal, Montreal, Canada

2. Medical University of Vienna, Vienna, Austria

3. Cliniques universitaires Saint-Luc, Université catholique de Louvain, Brussels, Belgium

4. Rechts der Isar Medical Center, Technical University Munich, Munich, Germany

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MEETING SUMMARY

The Bayer satellite symposium was introduced by Prof Fred Saad, who gave an introduction into the use of radium-223 in metastatic castration-resistant prostate cancer (mCRPC). Results from the recent Phase III ALpharadin in SYMptomatic Prostate Cancer (ALSYMPCA) study were also presented. Profs Kramer, Tombal, and Gschwend then each presented case studies on patients they had treated with radium-223. Each speaker also provided their own personal view and recommendations for use of radium-223 based on their experience with these patients. Prof Gschwend concluded the symposium with important considerations for the urologist in using radium-223 in mCRPC.

Investigating Clinical Practice With Radium-223 Dichloride in Metastatic Castration-Resistant Prostate Cancer to Optimise Patient Outcomes

Professor Fred Saad

The past 5 years have seen the emergence of several therapies for metastatic castration-resistant prostate cancer (mCRPC). Prior to 2010, androgen deprivation therapy (ADT) was the main treatment for non-metastatic disease while docetaxel was used in the metastatic castration-resistant setting.[1] Currently, multiple treatment options exist that can be used both in the chemo-naïve and post-chemotherapy settings. The availability of several therapies has improved our outlook on the outcome of mCRPC.

The bone is the most common site for metastasis in prostate cancer (PrC) patients.[2] Bone metastases are a significant cause of morbidity and

mortality and can significantly increase the risk of skeletal-related events (SREs) such as fractures.[2,3] In fact, SREs are associated with increased mortality in mCRPC patients with <1% experiencing a 5-year survival rate.[4] Radium-223 dichloride is the first alpha-emitting radionuclide that selectively binds to areas of increased bone turnover in bone metastases.[5,6] Being a calcium mimetic, radium-223 is able to be incorporated into newly formed bone material. The short range of the alpha particles means that toxic effects on adjacent healthy tissue and bone marrow are minimal, thus giving radium-223 a favourable safety profile.[5-7]

The ALSYMPCA (ALpharadin in SYMptomatic Prostate Cancer) study was a Phase III clinical trial that evaluated the effects of radium-223 on survival in mCRPC patients.[8] A total of 921 patients were randomised 2:1 to either radium-223 or placebo plus best standard of care. Radium-223 was administered as six injections at 4-week intervals. Patients were eligible to participate in the study if they had histologically confirmed progressive mCRPC with two or more bone metastases and no known visceral metastases. The primary endpoint was overall survival (OS). As many as 40% of patients had not received prior treatment with docetaxel, which enabled investigators to understand the effects of radium-223 in the chemo-naïve setting.[8]

The results of the study showed that median OS was improved in the radium-223 group compared to the placebo group (14.9 versus 11.3 months; hazard ratio [HR]: 0.70; 95% confidence interval [CI]: 0.58—0.83; p<0.001).[8] The results demonstrated a 30% reduction in the risk of death with radium-223 compared to placebo. Radium-223 was shown to improve all secondary endpoints significantly in comparison to placebo; it significantly prolonged both the median time to first symptomatic skeletal event (SSE) (15.6 versus 9.8 months; HR: 0.66; 95% CI: 0.52—0.83; p<0.001) and median time to prostate specific antigen (PSA) progression (3.6 versus 3.4 months; HR: 0.64; 95% CI: 0.54—0.77; p<0.001). Importantly, radium-223 was also able to delay the median time to increase in total alkaline phosphatase level (ALP) (7.4 versus 3.8 months; HR: 0.17; 95% CI: 0.13—0.22; p<0.001). Furthermore, a higher proportion of patients in the radium-223 group demonstrated a ≥30% reduction in ALP as well as normalisation at this level (p<0.001 in each case).[8]

Quality of life (QoL), as measured by the Functional Assessment of Cancer Therapy–Prostate (FACT-P) questionnaire, was also shown to be significantly improved in radium-223-treated patients.[8] Radium-223 also demonstrated a favourable safety profile, where the overall incidence of adverse events (AEs) was similar between the radium-223 and placebo groups.[8] Additionally, no clinically meaningful differences in the frequency of haematological AEs in patients receiving chemotherapy after radium-223 were observed between the study groups.[9] The strong efficacy and safety profile of radium-223 has led to its recommendation as a Grade A or Category 1 therapy for mCRPC in recent national and international guidelines.[1,10-13] Since initiation of the ALSYMPCA trial, additional PrC therapies have emerged onto the market, offering mCRPC patients multiple treatment options. Further research aims to find optimal combinations and sequences of existing therapies as well as tailoring treatment for individual patients.

Key Points

- The bone is a common site for metastases in PrC patients.
- Radium-223 is a novel agent shown to extend OS by targeting bone metastases in patients with mCRPC.
- The Phase III ALSYMPCA study showed that radium-223:
  - improved OS in mCRPC patients
  - caused a 30% reduction in the risk of death
  - improved the time to first SSE and time to PSA progression
  - has a favourable safety profile
- Radium-223 is recommended as a Grade A or Category 1 therapy for mCRPC in national and international guidelines.

Steering a Course in the Pre-Chemotherapy Setting: Insights From the Clinic and Patient Case Studies

Professor Gero Kramer

Results from the ALSYMPCA trial have shown that radium-223 has an OS benefit within the range of existing mCRPC treatments.[8,14-18] Radium-223 can be used in different disease settings including mildly symptomatic mCRPC as well as pre and post-chemotherapy. The case of a 64-year-old

patient diagnosed with mCRPC in 2009 was presented. The patient had an Eastern Cooperative Oncology Group (ECOG) performance status of 0, Gleason score 7 (4+3), and PSA 14 ng/ml. Upon diagnosis, the patient opted for alternative treatment consisting of thermo-immune therapy plus short-term ADT. In February 2012 the patient exhibited a tumour stage of pT3b pN1 M0, Gleason score 9 (4+5), PSA 7 ng/ml, and ultimately underwent radical prostatectomy. Four months later the patient presented with multiple bone metastases on the lumbar spine, thoracic spine, and ribs, and commenced treatment with degarelix and denosumab.

Following treatment, PSA decreased from 33 to 0.5 ng/ml but eventually progressed again despite therapy with bicalutamide. The patient started treatment with abiraterone but eventually had to stop this owing to PSA and radiographic progression. PSA levels were 290 ng/ml and a bone scan showed multiple bone metastases in the spine, bony pelvis, ribs, and femur. There were no lymph node or visceral metastases. The patient had mild pain (visual analogue scale [VAS] 2) in the lumbar spine but took no pain medication.

Prof Gschwend agreed that either option of radium-223 or chemotherapy was reasonable. Prof Tombal chose to treat with radium-223 as the patient had no visceral metastases and treating with radium-223 still gave the patient the option of having chemotherapy later. Prof Tombal went on to explain the importance of discussing treatment options with the patient and predicted that if patients know they have an alternative to chemotherapy then they are likely to opt for radium-223. However, it is important to bear in mind that patients with an ECOG performance status of 2 are unlikely to benefit from radium-223 treatment as their survival expectancy is <1 year. Prof Saad chose treatment with docetaxel due to the patient's quick progression as indicated by his PSA levels. Prof Kramer also opted for docetaxel and confirmed that this was the option presented to the patient.

However, the patient refused treatment with docetaxel and commenced radium-223 treatment instead. After two cycles of radium-223 treatment, PSA levels had still progressed from 879 to 1,009 ng/ml with ALP stable at 110 U/l. The patient had no visceral metastases. All speakers agreed that continuation with radium-223 would be the best option and Prof Kramer confirmed that this was the course of treatment chosen for the patient. Upon treatment with radium-223, the patient experienced an initial flare in PSA levels, however PSA eventually declined after the third cycle of treatment until the sixth cycle to a level of 524 ng/ml. ALP and bone alkaline phosphatase remained stable throughout the treatment period. After two cycles of radium-223 pains disappeared completely. Interestingly, prostate-specific membrane antigen positron emission tomography magnetic resonance imaging (PSMA PET MRI) did reveal an increase in activation of PSMA expression. Computerised tomography (CT) scans confirmed stable disease with no new metastases after six cycles of treatment and the patient did not suffer any side-effects.

In summary, this case study showed that radium-223 was well tolerated and that commencing treatment with radium-223 as soon as symptoms appear is appropriate. It also appears that radium-223 can be used in chemo-naïve patients with no visceral metastases. Although CT scans cannot be used to determine when to terminate radium-223 treatment, they should be done at intervals to monitor metastases. Multiple treatment options for mCRPC now exist and the best course of treatment should be determined by the individual patient profile, clinical symptoms, and patient preference.

Key Points

- Radium-223 can be used across the range of symptomatic mCRPC settings, e.g. pre or post-chemotherapy.
- Radium-223 may be considered in patients as soon as their bone metastases become symptomatic.
- Choice of treatment should be determined by the individual patient profile, clinical features, and patient preference.

Current Approaches in Monitoring mCRPC Treatment: Guiding Examples From Real-Life Patient Case Studies

Professor Bertrand Tombal

A patient case was presented of a 75-year-old man with ECOG performance status 0, Gleason score 7, and PSA 75 ng/ml. No metastases were observed and the patient was started on external beam radiation therapy plus degarelix. After 1 year

of hormonal therapy the patient experienced PSA progression and reported a pain score of 2/10 on the Brief Pain Inventory-Short Form (BPI-SF) questionnaire. A discussion ensued among the speakers as to the best course of therapy for this patient; treatment with docetaxel or abiraterone were considered the most suitable options. The current European Association of Urology (EAU) guidelines do not provide a clear-cut recommendation for the most effective drug for secondary treatment,[19] thus leaving the physician to decide the best course of treatment. Unlike abiraterone, enzalutamide, and radium-223, docetaxel does not have stringent criteria for use and can be used in patients with visceral metastases, small-cell PrC, and those taking analgesics.[8,15,17,20,21] The ability of docetaxel to be used in multiple disease states means that it is a widely used therapy for secondary treatment of mCRPC.

The two main treatment goals in mCRPC are prolonging OS and prolonging symptom-free survival. As many as 91% of mCRPC patients experience bone metastases, leading to SREs and SSEs which are often painful, thus reducing QoL.[20,21] Bone-targeted therapies, such as zoledronic acid and denosumab, have demonstrated a delay in the time to first SRE and decreased the total number of SREs during the lifetime of the patient.[22,23] Additionally, radium-223 has been shown both to decrease the incidence of SSEs as well as to prolong OS regardless of bisphosphonate use.[24]

This patient was a good candidate for treatment with radium-223 as he had bone metastases but no visceral metastases, and he had pain with radiological progression on abiraterone and experienced a moderate deterioration in ECOG performance status. After five injections of radium-223 an overall improvement was observed; ALP levels stabilised, pain decreased, and the patient reported an improved health status as measured by the EuroQOL five dimensions (EQ-5D) questionnaire. Continuing treatment of the patient will focus on maintenance therapy.

Radium-223 also offers several advantages as a therapy for mCRPC; it is a standard injectable and therefore straightforward to use, the patient can be released immediately following treatment, and the patient needs only to observe standard hygiene measures and does not need to undergo sterilisation. Contamination and accidental intake are unlikely, and exposure to other persons is negligible. In case of emergency surgery or security issues, patients carry a patient card stating that they have been treated with a radionuclide. In terms of practical considerations it is important for the urologist to decide on the choice of treatment in conjunction with the nuclear medicine physician. Once initiated, six cycles of radium-223 should be administered unless clinical deterioration or visceral metastases are observed. As there is no single marker to measure efficacy, it is recommended that both PSA and ALP are used alongside a pain scale such as the BPI-SF. It is also important to evaluate the health status of the patient by using a patient questionnaire such as the EQ-5D. Patient follow-up should be conducted every 3 months by a urologist or specialist nurse with monthly blood tests carried out to monitor toxicity.

Key Points

- The EAU guidelines do not provide a clear recommendation of therapy for secondary treatment of mCRPC, leaving physicians to decide on the best course of treatment.
- Patients with bone metastases but no visceral metastases are good candidates for radium-223 treatment.
- Patients should undergo six cycles of radium-223 unless clinical deterioration is observed.
- Radium-223 not only prolongs OS but also delays symptomatic skeletal events.

Outlook of the Changing mCRPC Treatment Landscape: Learning From Real-Life Experiences

Professor Jürgen Gschwend

Radium-223's favourable safety profile and unique mode of action means that it has potential to combine with novel anti-hormonal agents to treat mCRPC. Abiraterone potently blocks androgen biosynthesis and is also an inhibitor of CYP17, a key enzyme responsible for testosterone synthesis.[25] Enzalutamide works by blocking the binding of dihydrotestosterone to the androgen receptor, it also inhibits the nuclear translocation of androgen receptor and binding to DNA.[26]

Two patient case studies were presented in which radium-223 had been used in combination with other agents. The first case study presented was that of an 81-year-old man with newly diagnosed

metastatic PrC in July 2010. The patient had pelvic bone metastases, Gleason score 9 (4+5), PSA 54.5 ng/ml, ALP 230 U/l, and an ECOG performance status 0. The patient experienced no pain and was treated with complete androgen blockade for 30 months, which resulted in a decline in PSA. Following a diagnosis of mCRPC, denosumab therapy was initiated, however PSA progressed to 36.4 ng/ml. Therapy with bicalutamide was terminated and single androgen ablation therapy was maintained. The patient experienced another PSA rise to almost 50 ng/ml, ALP 220 U/l, and mild bone pain; in addition, small retroperitoneal lymph nodes (RLNs) were detected but no bone metastases.

In April 2013 the patient commenced treatment with abiraterone and prednisone. Although a rapid decline in PSA levels was observed, abiraterone treatment had to be terminated owing to peripheral oedema and cardiac insufficiency. However, due to progressing PSA levels, the patient started treatment with enzalutamide. After 10 months of abiraterone treatment and 1 month of enzalutamide, bone metastases were detected, small stable RLNs were present, and there was moderate bone pain, increasing PSA, and ALP 220 U/l. It was then decided to initiate treatment with radium-223. After six cycles of radium-223, PSA declined from 7.9 to 1.8 ng/ml. ALP also decreased towards more normal values. The patient also experienced an improvement in pain (maximum 2/10 VAS). Bone scans showed a decreased bone turnover and PSMA PET scans showed decreased PSMA uptake in the bone lesions.There was also no change in lymph node metastases. The patient had a good performance status (ECOG 0) and overall the treatment was well tolerated with no relevant side-effects.

The second case study described a 71-year-old patient who was diagnosed with bone prostatic hyperplasia and subsequently underwent a transurethral resection of the prostate. He was later diagnosed with PrC (Gleason score 6 [3+3]) and received bicalutamide treatment due to rising PSA (11.3 ng/ml). Despite this, the patient developed bone metastases in the spine and pelvis and was later treated with luteinising hormone-releasing hormone (LHRH) analogue and eventually also received palliative radiation due to bone pain.

After 19 months of receiving LHRH analogue, the patient was experiencing increasing pain (3/10 VAS) and a CT scan showed only small lymph node metastasis. The patient then commenced treatment with radium-223. After four cycles ALP levels declined; however, PSA levels increased from 58.1 ng/ml at the start of radium-223 treatment to 127.8 ng/ml. Pain levels decreased from 4/10 to 2/10 VAS. Due to concerns with the increasing PSA level, the patient initiated treatment with abiraterone and prednisone in addition to radium-223. This resulted in a rapid decline in PSA to 38.3 ng/ml with stable ALP. Clear remission was also observed in bone scans conducted after undergoing three cycles of radium-223.

Both of these cases demonstrate that radium-223 can be combined with abiraterone or enzalutamide and that this combination is well tolerated. However, further investigation in clinical studies is required. Importantly, PSA is not the main marker for response to radium-223; therefore, PSA decline should not be expected in every case. Treatment decisions should not only be based on PSA but should also take into account ALP, clinical features, level of pain, performance status, and patient wellbeing.

There are several ongoing studies investigating the effects of radium-223 in mCRPC. These include a Phase III study in combination with abiraterone and a Phase II study in combination with abiraterone and enzalutamide.[27,28] The effects of radium-223 in other solid tumour types (e.g. breast) are also being investigated.

Key Points

- The combination of radium-223 with novel antihormonal agents, namely abiraterone and enzalutamide, for the treatment of mCRPC appears efficacious and well tolerated, although prospective data will be needed to confirm this.
- There is no single robust marker for assessing treatment response to radium-223.
- Physicians should not expect to see a PSA response with radium-223. Impact on other traditional markers of treatment response (pain, ALP, radiographic progression) are mixed. Treatment with radium-223 should be continued through six cycles unless clear clinical progression or severe side-effects occur.
- Several clinical trials are further evaluating the effects of radium-223 in PrC and other solid tumours.

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