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Radium-223 Chloride

A New Treatment Option for Metastatic Castration-Resistant Prostate Carcinoma

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Abstract

In the last few years, the treatment of castration-resistant prostate carcinoma (CRPC) has changed completely. The approval of docetaxel and subsequent investigation in this field have led to development of new agents that have demonstrated an improvement in overall survival in the post-docetaxel setting, such as cabazitaxel and abiraterone. Radium-223 chloride is a radioisotope that has recently shown efficacy after docetaxel and in patients unfit for docetaxel, with improvements in overall survival and the time to the first skeletal-related event, compared with placebo, without increasing toxicity. These findings have made this agent a new option for treatment of these patients in the near future.

1. Introduction

Prostate carcinoma is the most common malignancy in men in Western countries, accounting for more than 240 000 cases in the US in 2011.[1] Although its mortality is relatively low compared with other malignancies, it is currently the second leading cause of cancer death in men, with more than 28 000 deaths in the US in 2011.[1]

Castration-resistant prostate carcinoma (CRPC) is defined by the following criteria: castrate serum levels of testosterone (<50 ng/mL); three consecutive rises in the levels of prostate-specific antigen (PSA) 1 week apart, resulting in two 50% increases over the nadir; antiandrogen withdrawal for at least 4 weeks for flutamide and for at least 6 weeks for bicalutamide; PSA progression despite consecutive hormonal manipulations; and progression or appearance of two or more bone lesions in bone scintigraphy, or in soft tissue, following the Response Evaluation Criteria In Solid Tumors (RECIST) criteria, or nodes >2 cm in diameter.[2] This progression occurs despite androgen deprivation therapy, and in this setting the estimated overall survival (OS) is about 18 months when docetaxel-based treatment is used.[3]

Nevertheless, this does not mean the tumor is fully resistant to subsequent hormonal therapies: that is why the term 'hormone-resistant prostate cancer' has been replaced by the term 'castration-resistant prostate cancer'. Even with castrate levels of testosterone, prostate cancer cells can still be hormone driven. Several studies have shown amplification and/or overexpression of androgen receptor (AR), intratumoral synthesis of androgens acting in a paracrine manner, and epigenetic alterations that influence AR activity.[4-6] Lowering of circulating testosterone levels is initially effective at blocking tumor growth, but prostate cancer will progress despite this.[7] In the past few years, several agents have been approved by regulatory agencies in the metastatic CRPC (mCRPC) setting post-docetaxel, such as abiraterone[8] and cabazitaxel.[9] Recently, a phase III trial of abiraterone in patients with mCRPC in the pre-docetaxel setting has also proven its superiority to placebo-prednisone.[10]

Because of the high skeletal morbidity of these patients, research has also focused on delaying or preventing skeletal-related events (SREs). Bisphosphonates, mainly zoledronic acid, have proven efficacy in this situation.[11] Recently, denosumab, a monoclonal antibody targeting the receptor activator of nuclear factor κB (RANK) ligand, has proven superior to zoledronic acid in delaying SREs, and in 2010 it was approved by the US Food and Drug Administration (FDA) for prevention of SREs in patients with bone metastases of solid tumors.[12] Specifically, denosumab prolonged the time to a pathologic fracture, spinal cord compression, radiation therapy to bone, and surgery to bone, as these were the events defined as SREs and analyzed in the trial.[12] With a different dosage and schedule of administration, denosumab has also been approved by the FDA as a treatment to increase bone mass in men at high risk of fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer. Table I summarizes agents that have a proven survival benefit in mCRPC.

Radium-223 chloride (223-Ra) is an alpha-emitting radiopharmaceutical that delivers high-energy irradiation with a short range, and therefore lower penetration into surrounding tissue than

Table I. Summarized view of agents with proven overall survival benefit in metastatic castration-resistant prostate cancer

	Docetaxel	Abiraterone	Cabazitaxel	Sipuleucel-T	MDV3100	223-Ra
MoA	Chemotherapy	Hormone therapy	Chemotherapy	'Cancer vaccine'	Hormone therapy	Alpha-emitting pharmaceutical
mCRPC indication	Treatment of CRPC (with prednisone)	Following docetaxel failure (with prednisone)	Following docetaxel failure (with prednisone)	Asymptomatic or minimally symptomatic mCRPC	No currently approved indication	No currently approved indication
Trial comparator	Mitoxantrone	Placebo	Mitoxantrone	Placebo	Placebo	Placebo
OS benefit	+2.5 months; HR 0.76	+4.6 months; HR 0.65	+2.4 months; HR 0.70	+4.1 months; HR 0.78	+4.8 months; HR 0.63	+2.8 months; HR 0.695
Efficacy endpoints with positive results	PSA, pain response, QoL	PSA, PFS, pain, time to first SRE	PSA, PFS		PSA, PFS	Time to SRE, PSA, ALP
Safety/tolerability	Neutropenia, anemia, alopecia, nausea, vomiting	Fluid retention, hypokalemia, hypertension, adrenocortical insufficiency	Neutropenia, leukopenia, anemia, diarrhea	Chills, fever, headache	Fatigue, seizures	Neutropenia, thrombopenia, diarrhea
Regulatory approval	2004 (US and EU)	2011 (US and EU)	2010 (US), 2011 (EU)	2010 (US)	Not approved	Not approved

223-Ra = radium-223 chloride; **ALP** = alkaline phosphatase; **CRPC** = castration-resistant prostate cancer; **HR** = hazard ratio; **mCRPC** = metastatic CRPC; **MDV3100** = enzalutamide; **MoA** = mode of action; **OS** = overall survival; **PFS** = progression-free survival; **PSA** = prostate-specific antigen; **QoL** = quality of life; **SRE** = skeletal-related event.

beta-emitting radiopharmaceuticals, such as samarium-153 and strontium-89.[13] In this review, we focus on the trials involving this radiopharmaceutical, from the initial phase I trial to the pivotal phase III trial recently presented at the European Society of Medical Oncology (ESMO) meeting in 2011.

2. Phase I Trial

This trial was published in 2005[14] and recruited a total of 25 patients with bone metastases from breast and prostate cancer (10 females and 15 males). Each of the patients received a single injection of 223-Ra, as part of a cohort dosage escalation schedule. Patients were included at each of the following doses: 46, 93, 163, 213, or 250 kBq/kg, and followed for 8 weeks. There was no dose-limiting hematotoxicity at any dosage level; reversible myelosupression occurred in some patients, with nadirs 2–4 weeks after injection and full recovery within the 8-week follow-up period. Two patients experienced grade 3 neutropenia; thrombocytopenia was observed only at level 1, even in the highest-dose patients. Other common adverse events (AEs) were transient diarrhea (in 10 of the 25 patients), bone pain, including a 'flare' effect (in 9 patients), nausea (in 5 patients) and vomiting (in 5 patients).

Seven of the 25 patients had a serious AE (SAE). Five of these were considered to be related to the extent of the malignant disease. One breast cancer patient experienced an episode of supraventricular arrhythmia, which was uncertainly related to the radiopharmaceutical (as the patient had a previous story of arrhythmia), and another breast cancer patient suffered from grade 3 vomiting and grade 3 leucopenia after treatment at the highest dose level, but made a full recovery.

An important finding was that alkaline phosphatase (ALP) levels were consistently reduced after 223-Ra injection, mostly in patients with elevated baseline levels, suggesting antitumoral activity and a possible prolongation of progression-free survival (PFS). Preclinical data also suggested antitumoral activity against skeletal metastases, leading to life extension.[15] Pain score data in this trial were improved with 223-Ra, with more than 50% of patients reporting benefits in pain control compared with baseline.

Therefore, 223-Ra was well tolerated at the studied doses, and data regarding pain control, little toxicity, and potential antitumoral activity led to further development of this agent.

3. Phase II Trials

The first phase II trial with 223-Ra, enrolling only CRPC patients, was published in 2007.[16] This trial included patients who were due to receive external-beam radiotherapy to relieve pain from bone metastases, and they were randomized to receive either four repeated monthly injections of 223-Ra, at a dose of 50 kBq/kg, or repeated injections of placebo, together with radiation therapy. The main objectives were a reduction in bone-specific ALP levels and prolongation of the time to occurrence of SREs.

Sixty-four patients were recruited between February 2004 and May 2005; 33 were assigned to 223-Ra and 31 to placebo. Twenty-eight patients in the 223-Ra group and 21 in the placebo group completed all four injections. The reasons for discontinuation were mainly progressive disease (in two patients in the 223-Ra group and four in the placebo group), patient preference (in four patients in the placebo group), cardiac disease (in two patients in the 223-Ra group and one in the placebo group) and confusion (in one patient in each group).

The median relative change in the bone ALP level from baseline to 4 weeks after the last study injection was −65.6% and 9.3% in the 223-Ra and placebo groups, respectively ($p < 0.0001$). This trial also included evaluation of the levels of other serum tumor markers, such as total ALP, procollagen-I N-propeptide (PINP), C-terminal crosslinking telopeptide of type I collagen (CTX-I), and type I collagen crosslinked C-telopeptide (ICTP), and they all were significantly reduced in the 223-Ra group.

The median time to the first SRE was 14 weeks in the 223-Ra group and 11 weeks in the placebo group. The hazard ratio for the time to the first SRE, adjusted for baseline covariates, was 1.75 ($p = 0.065$). The median relative change in the

PSA level from baseline to 4 weeks after the last study injection was −23.8% in the 223-Ra group and 44.9% in the placebo group ($p = 0.003$). The median time to PSA progression was 26 weeks for 223-Ra compared with 8 weeks for placebo ($p = 0.048$). The median OS was 65.3 weeks for 223-Ra and 46.4 weeks for placebo ($p = 0.066$), with an adjusted hazard ratio of 2.12 ($p = 0.02$). Myelotoxicity did not differ significantly between the two groups, and other side effects, such as vomiting, diarrhea, fatigue, or myalgia, were also similar. Only constipation was more frequent in the 223-Ra group.

The second phase II trial has been published very recently, in 2012.[17] This randomized, double-blind, phase II study aimed to investigate the dose-response relationship and pain-relieving effect of 223-Ra in CRPC patients with bone metastases. The primary endpoint was the pain index (according to a visual analog scale [VAS] and analgesic consumption), which was also used to classify patients as responders or non-responders.

Between May 2005 and December 2007, a total of 100 patients were randomized to receive different doses of a single injection of 223-Ra (5, 25, 50, or 100 kBq/kg). A statistically significant dose response occurred at week 2 ($p = 0.035$). At week 8, 40%, 63%, 56%, and 71% of the above dose groups, respectively, were pain responders (pain index ≤4). Of the responders, 30%, 42%, 44%, and 52% in the above dose groups, respectively, achieved a complete response (pain index 1) or a marked response (pain index 2). Up to week 8, fewer patients in the high-dose groups required increases in analgesia, compared with the lower-dose groups. Pain responders in all dose groups showed improvement in the Brief Pain Inventory (BPI) functional interference index. On the daily VAS at week 8, pain decreased by a mean of 30, 31, 27, and 29 mm in responders in the above dose groups, respectively.

About 97% of patients reported at least one AE. Hematologic events were generally not severe, with slightly greater rates of thrombopenia, leucopenia, and neutropenia in the two highest-dose groups. The most frequent hematologic AEs were anemia (11% of patients) and a hemoglobin decrease (15%). The most frequent non-hematologic AEs were nausea, vomiting, diarrhea, constipation, peripheral edema, and bone pain, with no difference across dose groups. Although survival was not an objective of this trial, the median OS was 50 weeks, which did not differ between dose groups.

These two trials suggested efficacy of 223-Ra in patients with mCRPC, in both symptomatic improvement and prolongation of survival, and with a favorable safety profile. These findings led to development of the placebo-controlled phase III trial ALSYMPCA (Alpharadin in Symptomatic Prostate Cancer).

4. Phase III Trial (the ALSYMPCA Trial)

The results of an interim analysis of the ALSYMPCA phase III trial were presented at the ESMO meeting in 2011 and are yet to be published.[18] This trial enrolled patients with confirmed symptomatic CRPC, with at least two bone metastases and no known visceral metastases, who had previously received chemotherapy with docetaxel or were unfit for docetaxel therapy. Patients were stratified according to ALP levels, previous bisphosphonate use, and prior docetaxel use. The primary endpoint was the OS. Secondary endpoints were the time to the first SRE, time to total ALP progression, total ALP response, total ALP normalization, time to PSA progression, safety, and quality of life (QoL).

A total of 921 patients were randomized on a 2 : 1 basis to receive 223-Ra at a dose of 50 kBq/kg, administered as six injections at 4-week intervals, or placebo. The interim results were analyzed after 314 events, and in light of these results the Independent Data Monitoring Committee (IDMC) recommended stopping the trial early because there was evidence of a significant OS benefit favoring 223-Ra.

The median OS was 14 months in the 223-Ra group versus 11.2 months in the placebo group (HR 0.695, $p = 0.00185$). The time to the first SRE was also longer in the 223-Ra group, 13.6 versus 8.4 months (HR 0.61, $p = 0.00046$). All of the other secondary endpoints also favored patients in the 223-Ra group. According to previous stratification factors, there was benefit across all subgroups in the 223-Ra treatment arm.

Eighty-eight percent of patients in the 223-Ra group and 94% in the placebo group presented with some kind of AE. Grade 3 or 4 AEs were seen in 51% of the 223-Ra group and 59% of the placebo group. SAEs were seen in 43% of the 223-Ra group and 55% of the placebo group. No AE was more frequent in the treatment arm than in the placebo arm.

Updated results of this trial were presented at the American Society of Clinical Oncology (ASCO) meeting held in Chicago (IL) in June 2012.[19] The OS benefit was consistent with previously reported data (14.9 vs 11.3 months, HR 0.695, $p = 0.00007$). Also, the time to the first SRE was significantly longer in the 223-Ra arm (12.2 vs 6.7 months, HR 0.64, $p < 0.0001$). No new safety signals were identified. Data regarding QoL are still pending.

5. Future Research Directions

The closing of the phase III ALSYMPCA trial may lead to early approval of 223-Ra by regulatory agencies in mCRPC patients. Its low toxicity profile and benefit in OS makes it a very attractive agent to test in tumors with a high occurrence of bone spreading, such as breast cancer.

In prostate carcinoma, 223-Ra is already being tested in CRPC patients in combination with docetaxel chemotherapy in a phase I–IIa trial (BC1-10 [A Study of Alpharadin® With Docetaxel in Patients With Bone Metastasis From Castration-Resistant Prostate Cancer (CRPC)]),[20] which was initiated in June 2010 and is being conducted in the US. The objective of this study is to establish the optimal dose of 223-Ra for this treatment combination, to confirm the safety of this strategy, and to explore potential efficacy. Safety and bone-marker data are expected throughout 2012.

In breast cancer, a phase II trial (BC1-09 [A Study of Alpharadin® in Breast Cancer Patients With Bone Dominant Disease no Longer Considered Suitable for Hormone Therapy]) is being conducted in endocrine-refractory patients with bone-dominant metastatic disease. This 23-patient open-label trial aims to elucidate the effect of 223-Ra in bone markers, and also the safety of this approach in breast cancer patients. At the 2011 San Antonio Breast Cancer Symposium, data for tumor makers were presented.[21] Patients were scheduled to receive four injections of 223-Ra at a dose of 50 kBq/kg every 4 weeks. Treatment with 223-Ra consistently reduced urine levels of NTX (N-terminal telopeptide) and bone ALP levels, and there were no SAEs related to the study drug. Functional imaging results, additional bone marker data, and patient-reported outcomes are being analyzed.

Several agents have been approved in the past few years or will probably be approved soon (table I). Cabazitaxel seems to be established as a chemotherapeutic option after docetaxel, at least until the results of the phase III trial comparing cabazitaxel with docetaxel as first-line therapy in mCRPC are known.[22] Although abiraterone is approved in the post-docetaxel setting, it will presumably move to the pre-docetaxel scenario in view of the results of the COU-AA-302 (Abiraterone Acetate in Asymptomatic or Mildly Symptomatic Patients With Metastatic Castration-Resistant Prostate Cancer) trial.[10] Another new hormonal therapy, MDV3100 (enzalutamide), was also proven to have OS benefit in mCRPC patients that have progressed on docetaxel in the phase III AFFIRM (Safety and Efficacy Study of MDV3100 in Patients With Castration-Resistant Prostate Cancer Who Have Been Previously Treated With Docetaxel-based Chemotherapy) trial;[23] there is also a phase III trial of this drug in the pre-docetaxel setting (PREVAIL [A Safety and Efficacy Study of Oral MDV3100 in Chemotherapy-Naive Patients with Progressive Metastatic Prostate Cancer]),[24] which is still enrolling patients. Therefore, combination and sequencing strategies will be critical for optimal management of these patients.

6. Conclusions

Radiopharmaceuticals in prostate carcinoma have traditionally been used with mainly a palliative intent, to improve symptomatic control in patients with bone metastases. These drugs also have considerable toxicities, mostly hematologic, that could cause SAEs and also handicap future therapeutic possibilities.[25,26] None of the pre-

viously tested agents, such as samarium-153 or strontium-89, have clearly demonstrated a benefit in OS.

223-Ra, an alpha-emitting agent, has recently shown a consistent effect on OS in mCRPC patients after progression on docetaxel, or in patients unfit for docetaxel therapy, and symptomatic relief and prolongation of the time to the first SRE were significantly greater with 223-Ra therapy. Therefore, it has become a new therapeutic option in this setting and hopefully will be available within a short period of time.

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