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Role of Radium-223 in the Treatment of Metastatic Castration Resistant Prostate Cancer (Mcrpc): Clinical Practice and Future Perspectives

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Abstract

The therapeutic landscape for patients with Metastatic Castrationresistant Prostate Cancer (mCRPC) has rapidly changed in the last 5 years. New hormonal, cytotoxic and immunological agents have been introduced demonstrating efficacy both in terms of cancer control and survival improvement. 223Ra-dichloride (Radium-223), is a calcium-mimetic alpha emitting radiopharmaceutical agent with a very high linear energy transfer,able to determine an irreversible damage in the DNA of cancer cells. In a large controlled randomized perspective clinical trial, Radium-223 provided interesting results in symptomatic mCRPC patients with bone metastases, by decreasing pain, delaying Skeletal Related Events (SREs) and improving the survival. Among a series of radiopharmaceuticals for the treatments of skeletal metastases (i.e. Strontium-89, Rhenium-186 and Samarium-153) in prostate cancer patients, Radium-223 is the first agent that demonstrated a favorable impact on bothimprovement of quality of life and overall survival.

This overview discusses the current armamentarium available for mCRPC patients, focusing the attention on Radium-223, its selective uptake in bone metastases, the safety profile and the open questions related to its use in clinical practice, such as the doses and the number of cycles of treatment. Moreover, being themechanism of Radium-223 action not potentially in overlap with any other available treatments, it results suitable for both sequencing and combination studies. In the present paper, future perspectives are briefly discussed by the authors considering some possible associations of Radium-223 with other therapeutic agents that would improve the outcomes of patients without increasing toxicities, and by looking for its potential applications in the next future.

Keywords: Castrate resistant prostate cancer; Bone metastases; Radium-223; Radio metabolic therapy

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Introduction

Prostate Cancer (PCa) is the second most commonly diagnosed cancer in men and accounts for nearly 20% of all newly diagnosed male tumors. At diagnosis, approximately 80% of patients present with localized PCa and 4% with distant metastases: the 5-year relative survival rate is 100% and 28% respectively [1]. Due to cell growth dependence on androgens, Androgen Deprivation Therapy (ADT) is the standard of care for advanced or metastatic PCa patients. However, following initial response to ADT, approximately 10-20% of patients (and virtually all patients with metastatic disease) will develop Castration-Resistant Disease (CRPC), an incurable condition with a median survival of <3 years [2]. More than 90% of men with Metastatic Castration-Resistant Prostate Cancer (mCRPC) have radiological evidence of bone metastases [3], often leading to symptomatic skeletal events with pain and bone fractures [3-6]. Anemia accompanies advancing disease and is a risk factor for poor outcome in mCRPC [7,8]. Since 2004, docetaxel in combination with prednisone has been the standard therapy for patients with mCRPC [9-12]. However, in the last 5 years, several new agents with different mechanism of action have become available for the management of these patients. These compounds includea new taxane, cabazitaxel, the second-generation hormonal

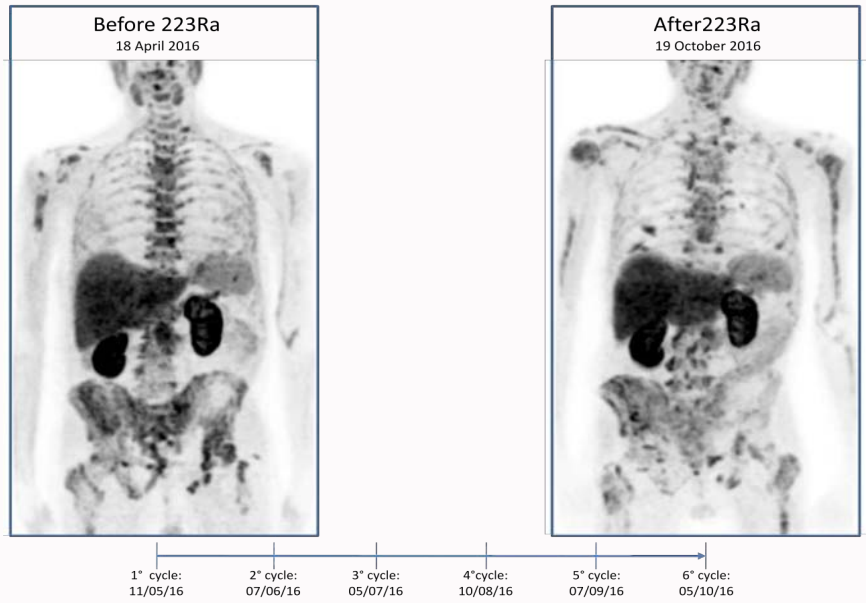

Figure 1: Bone scan before (A) and after 5 cycles of ^{223}Ra-treatment (B) in a 76-year old patients with castrate resistant prostate cancer.
Figure 2: ^{18}F-Choline PET/CT scan in a 69-year old patient before (A) and after 6 cycles (B) of 223Ra-dicholoride therapy.

agents abiraterone and enzalutamide, and the alpha emitter Radium-223 [13-20].

Improving options for patients with mCRPC requires a different approach to each patient, to offer the most appropriate therapy. A multidisciplinary team should follow the patient with prostate cancer since diagnosis, to integrate the different professional knowledge and skills and to plan an optimal patient treatment [21]. In the last years, there has been increasing interest for radiopharmaceutical agents able to specifically target the bone or the cancer [22]. Several treatment modalities are used to control metastatic bone pain or prevent Skeletal-Related Events (SREs) from PCa, such as radiotherapy, 186-Rh and 153Sm-ethylene diamine tetra methylene phosphonate, bisphosphonates, denosumab and other bone-seeking agents; however, only Radium-223 has demonstrated to improve survival, showing not only a bone targeted action, but also an antineoplastic effect [20,23,24-27].

Radium-223 dichloride (Radium-223) is a calcium mimetic that specifically targets newly formed bone in areas of osteoblastic metastases. It decays by emitting high-energy alpha particles causing predominantly on-repairable double-stranded DNA breaks in tumor cells [28-30]. Tissue penetration is minimal, resulting in highly localized cell killing with negligible damage to surrounding healthy tissues including bone marrow cells [28,29]. Unlike External Beam Radiation Therapy (EBRT) and beta particle emitting radionuclides indicated for pain palliation, the short range of therapeutic radium-223 alpha particles spares hematologic tissue, which may result in fewer hematologic Adverse Events (AEs) [31].

Role of the Multidisciplinary Team

Since 2010, the approval of cabazitaxel, oral agents abiraterone acetate and enzalutamide and Radium -223 has expanded dramatically the treatment options for mCRPC patients, resulting in longer survival and improved quality of life [8,15-18,20].

Patient selection, the opportunity to combine treatments with other modalities, and the optimal treatment sequencing are still matter of debate. Furthermore, counseling on patient expectations in terms of prognosis and quality of life is becoming more and more important in formulating the best individual treatment plan. For these reasons, a multidisciplinary approach should become the standard of care for the treatment of patients with mCRPC; specialized urologists, medical oncologists, radiation oncologists, nuclear medicine physicians, pathologists, imaging specialists, psychologists, experts in rehabilitation, experts in supportive and palliative care, geriatricians [32,33] should work together in a structured patient-focused multidisciplinary setting. These figures have a specific role depending on the patient's disease state and, to be effective and efficient, the various members should be organized taking into consideration the different phases of the disease and associated treatments. Synchronous counseling avoids separate meetings and reduces patient anxiety (Figure 1).

Therapeutic Landscape in mCRPC

Chemotherapy

In 2004 two pivotal trials have demonstrated the possibility for chemotherapy to achieve not only disease palliation (until that date, the only documented efficacy for mitoxantrone chemotherapy was palliation), but also to have a statistically significant effect on patient survival. The SWOG 99-16 trial randomized patients to receive either mitoxantrone and prednisone, or the combination of docetaxel plus estramustine phosphate [14]. The TAX 327 trial compared the combination of mitoxantrone and prednisone versus docetaxel and prednisone [13]. In this study docetaxel was given at two different schedules, i.e. either weekly or 3-weekly.Both studies showed that docetaxel combinations were significantly superior to mitoxantrone and prednisone in Overall Survival (OS). It is difficult to compare these two landmark trials. However, the addition of estramustine seems to add no benefit, while increasing toxicity [14]; therefore, the 3-weekly docetaxel schedule was approved as the recommended front-line regimen for mCRPC. Subsequent analysis of the TAX 327 trial has demonstrated the superiority of docetaxel plus prednisone combination in all patient subgroups, irrespectively of age, tumor

burden, site of metastasis, bone involvement and the presence of disease related symptoms [34].

In more recent years, cabazitaxel, a semi synthetic analog of docetaxel, has been approved for mCRPC patients progressing during or after docetaxel treatment. The TROPIC trial was a randomized trial comparing mitoxantrone versus cabazitaxel, both in combination with low dose prednisone, in 755 patients after first line treatment with docetaxel and prednisone. This study showed a statistically significant OS advantage in favor of cabazitaxel (15.1 *vs.* 12.7 months, p <0.0001). Cabazitaxel documented also significant better outcomes for PSF, objective response of measurable disease and PSA response. However, pain control was comparable in the two arms and a higher number of adverse events occurred in the cabazitaxel arm [15]. Hematological toxicities were more frequent and severe; therefore a careful patient selection and appropriate prophylactic use of G-CSF should be considered when using this agent [35].

Second generation hormonal therapies

Until recently, options for the management of CRPC patients have been limited to second-line attempts with agents like corticosteroids, high dose estrogens, ketoconazole. The use of these compounds, which have been shown to benefit no more than 30% of patients without any clear advantage in survival, was made on empirical bases [36]. Over the past few years, the driving role of AR has been evidenced even in the castration resistant disease setting, because of genetic alterations, either amplification or mutations, of the Androgen Receptor (AR), which can allow tumor growth still driven by the binding of amplified/ mutated AR with residual androgens. In this context, new endocrine therapies have been developed.

Abiraterone acetate is a potent, selective and irreversible inhibitor of 17-alpha-hydroxylase and C-17, 20-lyase CYP17 activity, thereby blocking non-gonadal production of androgens. It is associated with low dose corticosteroids to minimize the incidence and relevance of side effects like hypertension and hypokalemia. The COU-AA 301 trial compared abiraterone plus prednisone versus prednisone plus placebo in patients with docetaxel-pretreated mCRPC; this trial showed a definite superiority of abiraterone over placebo both in terms of OS (with a median of 14.8 months in the abiraterone group *vs.* 10.9 months in the placebo group; p <0.00001) and in terms of radiologic progression (5.6 months *vs.* 3.6 months, respectively), PSA response (29% *vs.* 6%) and pain control (44% *vs.* 27%) [16]. Abiraterone acetate was more effective in decreasing the incidence and severity of SREs. Side effects were generally mild, with a low rate of discontinuations. Based on these results, the COU-AA 302 trial was conceived to investigate the role of the drug in docetaxel-naïve patients with mCRPC. The selected patients had asymptomatic or mildly symptomatic disease and no evidence of visceral metastases. Abiraterone was statistically superior to prednisone, either in terms of OS (34.7 months *vs.* 30.3 months; p <0.003) and in terms of radiological PFS (16.5 months *vs.* 8.3 months; p <0.001). The incidence of side effects in the two treatment groups was comparable to that observed in COU-AA 301 study, with a significant increase in cardiac disorders (19% *vs.* 16%) and altered liver function tests (12% *vs.* 5%) in the abiraterone arm [16,17].

Enzalutamide is a new potent anti-androgen, with no agonistic activity and a greater affinity for the AR than first generation anti-androgens like fltamide or bicalutamide. It also acts on nuclear translocation and DNA binding of AR. The AFFIRM trial enrolled 1199 patients affected by mCRPC progressed under or after a treatment with docetaxel [18]. Patients were randomized to receive enzalutamide or placebo. At a median follow-up time of 14.4 months, median OS was 18.4 months in the enzalutamide group *vs.* 13.6 months in the placebo group (HR: 0.63; 95% CI: 0.52-0.75; p< 0.0001). Time to radiological progression (8.3 months *vs.* 2.9 months) and time to PSA progression (8.3 months *vs.* 3 months) also statistically favored the enzalutamide arm. A significant impact on the incidence and severity on SREs was observed with enzalutamide. More patients assigned to enzalutamide experienced fatigue, diarrhea, muscle-skeletal troubles and hot flushes, and five patients assigned to enzalutamide developed seizures [18].

Enzalutamide was evaluated in chemo-naïve patients in the PREVAIL trial; 1680 patients with asymptomatic or mildly symptomatic mCRPC were randomized to receive either enzalutamide or placebo. A significant increase in OS and radiological PFS was documented. An advantage in favor of enzalutamide was also shown in respect to time to chemotherapy initiation (HR=0.35), time to first SRE (HR 0.72) and time to PSA progression (HR 0.17) [19].

Zoledronic acid and denosumab

Zoledronic acid is the only bisphosphonate that has demonstrated significant efficacy and long-term clinical benefit by preventing SREs in patients with PCa. The administration of zoledronic acid (4 mg every 3 weeks) versus placebo in 643 mCRPC patients resulted in a reduction of the number of patients having aSRE (33% *vs.* 44%; P = 0.021). It also showed improvements in pain and analgesia scores but there were no differences in disease progression or OS [37-40].

Denosumab is a fully human monoclonal antibody directed against RANKL, the main driver of osteoclast formation, function, and survival. It acts inhibiting osteoclast-mediated bone destruction, decreasing bone re-absorption and increasing bone mass. The drug is administered via subcutaneous injection. A phase III trial on1, 904 mCRPC patients compared denosumab (120 mg administered subcutaneously every 4 weeks) with zoledronic acid (4 mg intravenously every 3 weeks) [41,42]. Denosumab prolonged the time to first SRE by 3.6 months (20.7 months *vs.* 17.1months; HR=0.82; P <0.001 for non-inferiority, P = 0.008 for superiority). The two groups had similar OS and time to disease progression. OS, disease progression, and rates of AEs and serious AEs were similar in the two arms, but denosumab had an increased incidence of hypocalcemia (13% *vs.* 6% in the zoledronic acid group; P <0.0001).

Beta Emitters

Until a few years ago, nuclear medicine proposed some beta-emitting agents for the treatment of bone metastases, such as Strontium-82, Samarium-153 and Rhenium-186, that demonstrated only a palliative action in patients with diffuse skeletal disease [22]. Rhenium-186-HEDP Imaging of the 155 keV gamma photon is an advantage which provides an opportunity for estimation of radiation dose to metastatic sites. Beta Emitters Strontium-89and Samarium-153 documented an advantage in pain palliation and no benefit on survival. As β-emitters have a track length in the order of millimeters, their use for the palliation of bone pain from metastases has been limited by bone marrow toxicity [43]. A systematic review and meta-analysis of clinical studies involving strontium-89 and samarium-153 showed overall efficacy of 70% for both agents in reducing metastatic bone pain in mCRPC patients and complete pain relief in 27% of patients (REF). Dose-response studies have shown increasing rates of response to pain and increasing myelotoxicity with

increasing doses of samarium-153, limiting the use of higher doses [44,45].

A phase 3, placebo-controlled Canadian clinical trial evaluating the efficacy of a single 10.8 mCi injection of strontium-89 as an adjuvant to local-field radiotherapy in mCRPC patients(n = 126) documented asignificant delay in pain progression, producing as expected higher hematologic toxicity involving leukocytes and platelets. Complete pain response was observed in 30–60% of treated patients, with no statistically significant difference in survival [46,47]. Samarium-153 showed pain palliation in 152 patients with mCRPC and painful bone metastases in a pivotal phase 3 trial [48]. A statistically significant reduction in opioid use, suggesting pain reduction, was observed at treatment weeks 3 and4. In the TRAPEZE phase 2/3 trial in 757mCRPC patients, strontium-89 treatment after 6 cycles of docetaxel improved clinical progression-free survival (HR 0.85; 95 % CI 0.72–0.99; p = 0.036) [49]. A phase 2 trial of a consolidation regimen of samarium-153-EDTMP with docetaxel in mCRPC after docetaxel and hormonal therapy, showed that the combination was well tolerated and produced sustained pain relief and a PSA response [50,51]. Samarium-153 was safely used in prostate cancer patients who had prior chemotherapy or radiotherapy (REF).

Radium-223

Radium-223 (^{223}Ra), a first-in-class alpha-emitting radiopharmaceutical, is an alkaline earth element and acts like a calcium mimetic: it is absorbed into bone matrix at sites of osteoblastic activity. The half-life of ^{223}Ra is *t1/2* = 11.4 days, leading to interest in its use in cancer treatment as the drug can be delivered to the site of bone disease and continue to deliver dose. Radium-223 decays to the stable isotope of lead, ^{207}Pb, in six steps. Of the energy emitted, 95.3% decays as alpha radiation with 3.6% and 1.1% as beta and gamma radiation, respectively. It is possible to detect photon emissions from the decay of Radium-223 using standard techniques. Alpha particles penetrate tissue only to a depth of 2-10 cell diameters (<100 micron), leading to highly localized cell killing and minimal damage to normal tissues. The favorable path length of the emitted radiation warrants therefore bone marrow sparing.

After intravenous injection, ^{223}Ra is cleared rapidly from the blood; only 6% of initial activity is seen in the blood by 1-hour post-injection, less than 1% at 24hours. Excretion is predominantly via the gastrointestinal tract with minimal (approximately 5%) early urinary excretion [52,53]. Evidence that 223Ra accumulates in the bones has been demonstrated by scintigraphy in phase I trial. Low external dose rates [54] allow for patient release from radiation control measures immediately following administration. Minimal prudential restrictions on family contacts are therefore needed after treatment with ^{223}Ra. As there is also some blood and urine activity, caution is recommended with body fluids and stool for one week after drug injection.

^{223}Rahas documented a safe profile in a phase I trial, with no observed DLT [28-30]; the MTD was not reached in CRPC patients and metastatic breast cancer patients treated at different dosing schedules. Phase I and phase II trials have shown the safety of the drug and the effectiveness on alkaline phosphatase (ALP) reduction and pain reduction. The pivotal trial ALSYMPCA demonstrated an OS benefit of ^{223}Raas compared to placebo administration for patients with symptomatic bone metastases from mCRPC. Enrolled patients had at least two bone metastases at bone scan and no visceral disease on CT scan; lymph node disease up to 3 cm of diameter in short axis was allowed. They should have received docetaxel, or be unfit for chemotherapy or have refused it. Symptomatic disease was defined including patients with regular assumption of analgesic medication (non-opioid or opioid) or pain-free patients who had received EBRT for cancer-related bone pain in the 12 weeks before randomization. At baseline, 44% of ^{223}Raand 45% of placebo patients had no pain or had mild pain effectively managed without need for opioids. Patients in the non-opioid subgroup presented less advanced disease: a greater proportion with ALP values <220 U/l, lower median ALP and lactate dehydrogenase values, better performance status, less extensive skeletal disease, fewer prior docetaxel therapy and EBRT for pain. Enrolled patients were stratified in accord with previous chemotherapy (yes *vs.* not), concomitant bisphosphonate use (yes *vs.* not) and ALP baseline level. In this randomized phase 3 study, ^{223}Raplus best standard of care (BSoC) versus placebo plus BSoC prolonged median OS by 3.6 mo (Hazard Ratio [HR] = 0.70; 95% confidence interval [CI]: 0.58–0.83; p <0.001; median 14.9 mo *vs.* 11.3 mo, respectively): The effectiveness of ^{223}Rawas documented in all the stratified subgroups. ^{223}Ra also prolonged median time to first Symptomatic Skeletal Event (SSE) by 5.8 mo (HR = 0.66; 95% CI: 0.52– 0.83; p <0.001; median 15.6 mo *vs.* 9.8 mo, respectively) [20,55]. These results led to ^{223}Ra approval for the treatment of mCRPC patients with symptomatic bone metastases and no known visceral metastatic disease.

Patients receiving ^{223}Rahad a meaningful improvement in quality of life as defined by an increase of ≥10points on a scale of 0 to 156 on the FACT-P questionnaire (25% *vs.* 16% for ^{223}Ra and placebo respectively; P = 0.02). The survival duration and time to first SSE were longer in minimally symptomatic (ie., WHO ladder pain score 0–1/without opioid use) than in more symptomatic patients (ie., WHO ladder pain score 2–3/ with opioid use). These data suggest that appropriate timing of ^{223}Ra treatment should not be based on symptom severity and that using ^{223}Ra earlier may optimize clinical outcome and allow sequencing with other effective therapies. In addition, ^{223}Ra treatment significantly delayed time to first opioid use and reduced the need of EBRT for bone pain, but ALSYMPCA was not designed to evaluate the effect of ^{223}Ra on pain, since the primary endpoint was OS. Accordingly, any observed pain response or lack of response should not be considered a cause to prematurely stop ^{223}Ra treatment.

Radium-223had a favorable safety profile, with a low overall incidence of grades 3-4 myelosuppression and fewer AE and SAE than placebo arm [20]. The drug was well tolerated, regardless of prior docetaxel exposure. No differences were seen in the safety profile between patients who did and did not receive concomitant EBRT for bone pain during the study.

The most important recorded toxicities were minor gastrointestinal side effects and mild neutropenia and thrombocytopenia [20]. No significant differences were reported between treatment arms in anemia, as this event was mainly related to baseline extent of bone disease. A number of ≥6 bone metastases was associated with increased risk of grade 2 – 4 anemia (HR = 1.52; 95% CI: 1.17 – 1.97; p = 0.002). The number of blood transfusions and time to first blood transfusion were similar among the two groups [31]. Risk for developing G2-4 neutropenia was related to prior docetaxel therapy, higher WHO pain score and decreased baseline neutrophil count; platelets decrease was related to previous docetaxel administration and lower basal level of

platelets and hemoglobin: these features were generally associated to a higher extent of disease, and to higher ALP level and bone pain. Platelets transfusions were more frequently administered to ^{223}Ratreated patients, mainly after third cycle, suggesting a cumulative effect and advising clinicians to carefully evaluate the benefit and risk of continuing treatment.

It is important to identify potential risk factors for hematologic toxicity before ^{223}Ra initiation, to monitor high-risk patients for treatment modifications [31]. The maximum efficacy of treatment is associated to completion of 6 injections administration, and as above mentioned the tolerability is better in presence of adequate level of ALP, hemoglobin and platelets, and in patients with lower extension of skeletal disease and mild pain [20,56]. Current international guidelines recommend ^{223}Ra as an option in both pre- and post-docetaxel settings, and it is possible to administer ^{s}Rain patients with bone metastases also as first line therapy for mCRPC [57,58]. No safety concern was identified in an exploratory analysis of prospectively collected data from ALSYMPCA trial on patients that received subsequent chemotherapy after ^{223}Raor placebo [59]. Most analyzed patients had also received docetaxel prior to ^{223}Ra. No significant differences were underlined between treatment groups in frequency of grade 3-4 hematological adverse events, indicating that the use of chemotherapy following ^{223}Ra is feasible regardless of prior docetaxel use [59], and, most importantly, that prior treatment with ^{223}Rado not compromise the efficacy of subsequent chemotherapy. This observation strengthens the possible use of 223ra as first line approach, when tumor burden is limited, hemoglobin level adequate and patient is more likely to complete the planned treatment.

Overall, the treatment is safe also in a long-term period of observation: at the end of the 3-year follow-up period, no reports of acute myeloid leukemia, myelodysplastic syndrome or new primary bone cancer are known [22]. A study exploring the benefit of retreatment with ^{223}Ra in 44 patients who have already received 6 cycles documented a lower number of hematological events than in the ALSYMPCA trial. Besides prior 223Ra, all patients had received previously ≥2 hormonal regimens; 45% had been pretreated with ≥1 chemotherapy regimen. Overall, their baseline characteristics were comparable to ALSYMPCA. Twenty-nine (66%) completed all the 6 retreatment injections. No new safety concerns were noted; only 2 patients had grade 3 hematological adverse events. Only one patient had radiographic bone progression, with a median rPFS of 9.9 months [59].

The international Expanded Access Programme (EAP) was a phase 3b trial conducted after ALSYMPCA and before regulatory approval; the endpoints were safety and OS. A total of 839 patients with bone metastases (at least two lesions) from CRPC and without visceral disease were enrolled. Lymph nodes were allowed up to 3 cm in diameter, and patients could be treated independently if symptomatic or asymptomatic. Also concomitant anticancer therapies were allowed. Overall, 696 patients received at least one dose of Ra223 and were evaluated for safety. Grade 3-4 anemia occurred in 5% of patients, thrombocytopenia in 2% and neutropenia in 1%. Median OS was 16 months, and it was longer for patients with normal ALP than for patients with higher ALP levels; for patients with baseline hemoglobin level of 10g/dL or greater versus patients with lower Hb; for patients with ECOG PS of 0 compared to ECOG PS 1; and for patients with no reported baseline pain versus symptomatic patients. Median OS was also better in patients receiving concomitant denosumab and in patients with concomitant administration of ^{223}Ra and enzalutamide or abiraterone acetate [56]. These observations confirm the data on efficacy and safety reported in the registration trial, and reinforce the magnitude of benefit in the early use of the drug. Furthermore, preliminary evidence of feasibility and efficacy of combination therapies with ^{223}Ra and new-generation antiandrogens was shown.

Disease Evaluation with Radium - 223

More patients in the ^{223}Ra group had a ≥30% reduction in the total ALP and PSA than in the placebo arm. A significant prolongation in time to increase in ALP was seen with ^{223}Ra compared to placebo (7.4 months *vs.* 3.8 months respectively; HR 0.17; 95% CI 0.13 to 0.22; P <0.001). There was no significant difference in time to PSA progression. PSA test should not be used to measure response during therapy with ^{223}Ra, because its level typically continues to rise during the early phase of treatment courses. A decline in PSA level is usually observed in responding patients after 4 or 5 months of treatment, which is too late for assessing response. As evidenced in recent case reports [61], we recommend not to discontinue 223Ra therapy on the occurrence of an asymptomatic PSA rise not supported by a radiological report of disease progression. During ^{223}Ra treatment, PSA flare phenomenon can be misinterpreted as therapeutic failure.

In contrast, a decrease in the ALP levels in responding patients is almost always observed during treatment with ^{223}Ra. It is important to recognize this phenomenon in clinical practice, to avoid early discontinuation of an ongoing and potentially effective treatment. Bone biomarkers such as ALP should be integrated in clinical evaluation; furthermore, morphological imaging (CT scan and multimodal MRI) and metabolic techniques targeting bone (^{99m}Tc-HDP WB bone scan and ^{18}F-Fluoride PET/CT) can provide important information.

Of note, bone scan could be confounder as PSA due to the bone flare phenomenon that can wrongly be misinterpreted for disease progression.

In this setting, nuclear medicine offers today different radiopharmaceutical options for the detection of metastatic PCa. We can divide them in two main subsets: bone targeting (i.e. ^{99m}Tc-phosphonate and ^{18}F-Fluoride) and cancer targeting agents (^{11}C/^{18}F-Choline, ^{18}F-FDG, ^{68}Ga-PSMA, ^{18}F-FACBC, and ^{11}C-Acetate), although some of them are still considered as experimental and therefore not applicable in clinical practice.

In the ALSYMPCA trial a bone scan and a CT scan were performed to evaluate patients for enrollment; however, no imaging modalities were scheduled during and after treatment. So how to evaluate these patients is still matter of debate. There are no established criteria to evaluate bone disease; in fact, RECIST criteria consider bone metastases as non-target lesions [62]. According to the PCWG3 criteria [63], focused on clinical evaluation, and to the St Gallen Advanced Prostate Cancer Consensus Conference (APCCC) [36], the clinical benefit should represent the most important criteria of response to treatment.

Imaging and Radium-223

The role of imaging in patients candidates to ^{223}Ra has twice objective: a) to select appropriate subjects before to start the therapy and b) to monitor the early and delayed evaluation of response to treatment.

As reported by ALSYMPCA trial [20], patients without any visceral involvement and with the lymph node metastases less than 3 cm in diameter can be submitted to Radium-223 treatment. More often, these criteria can be assessed by using three-phase contrast enhancement Computed Tomography (CT). However, the evaluation of bone involvement by CT, is scarce thus requiring more sophisticated or specific imaging such as bone scintigraphy with ^{99m}Tc-diphosphonate. In the last years, some papers have been published about the role of bone scintigraphy in patients who are candidates to ^{223}Ra, for evaluating 1) the extension of disease, 2) the response to treatments and 3) the hematological effects of ^{223}Ra treatments in patients with high load of disease [64,65]. As reported by Nome et al. [65], the post ^{223}Ra treatment reduced uptake of ^{99m}Tc-diphosphonate may reflect a diminished tumour burden, as well as a direct radiation effect on the osteoblasts (stunning or cell death) (Figure 1). However, small or microscopic bone metastases surrounded by no or minimal osteoblast activity, and therefore no major uptake of ^{223}Ra, are not sufficiently irradiated and may thus increase in size, resulting in new sites of ^{99m}Tc-diphosphonate uptake on the post-treatment bone scans. To overpass this latter phenomenon, the same authors suggested to use PET/CT systems that have much higher geometric resolution than conventional gamma cameras, and will detect smaller lesions and therefore more lesions than conventional bone scans. ^{18}F-Fluoride PET/CT is an alternative imaging modality for the assessment of bone metastases in patients with metastatic prostate cancer.

Last studies reported the advantages of ^{18}F-Fluoride PET/CT in patients treated with ^{223}Ra-dichloride, because a close correlation between the magnitude of reduction in tracer uptake and ALP was seen [66]. Furthermore, as for bone scintigraphy, also ^{18}F-Fluoride PET/CT can determine which patients will benefit from ^{223}Ra and which will develop bone marrow failure [67]. Few data are now available about PET/CT with ^{11}C/^{18}F-Choline, ^{68}Ga-PSMA and ^{18}F-FACBC before and after ^{223}Ra treatment (Figure 2).

Some preliminary results demonstrated more advantages of cancer targeting tracers (i.e. ^{68}Ga-PSMA or ^{11}C/^{18}F-Choline) than bone targeting ones (i.e. ^{18}F-Fluoride) [22,68, 69]. In fact, cancer targeting radiopharmaceutical agents can assess both the metabolism of cancer at bone level and in the viscera (e.g. lung, liver and lymph nodes). Moreover, cancer targeting agents are less influenced by flare phenomenon than bone targeting radiotracer.

The flare phenomenon, defined as an increase in the number or intensity of bone lesions with subsequent improvement while the patient is receiving systemic therapy, have been already reported during ^{223}Ra treatment for the pain (phase I trial), for the PSA levels and for ^{18}F-Fluoride PET/CT [66]. Nuclear imaging modalities offer different alternatives for the evaluation of patients who are candidates to or treated with ^{223}Ra-dicholide, but few established data are now available. Moreover, comparative data among imaging morphological modalities like CT, functional imaging strategies like MRI and metabolic imaging such as PET/CT with different radiotracers are necessary for better understanding the advantages from sophisticated imaging systems.

Discussion

In the last 5 years, the treatment landscape for patients with mCRPC has rapidly changed. Besides Radium-223, new hormonal, cytotoxic, and immunotherapeutic drugs have demonstrated improvement in OS by randomized trials. Therefore, the identification of the optimal treatment strategy, how to define the therapeutic sequences and how to quantify or assess the response, in each single patient, need to be explored.

The benefit observed with ^{223}Ra is similar to that seen with the other life-prolonging drugs. Most men with mCRPC are likely to receive all these treatments, although the optimal sequencing and combinations are matters of debate. ESMO recently validated a reproducible tool to measure the magnitude of clinical benefit obtained from various therapies for solid tumors. To evaluate the benefit of treatments, outcomes like survival, quality of life, and toxicity were used [70]. Interestingly, Radium-223 was the only treatment for PCa that has received the maximum score of 5. This score for ^{223}Ra may be ascribable to documented improved OS, improved time to SSEs, better quality of life, and reduced need for hospitalization. ^{223}Rais often relegated to late-stage mCRPC, consistently with the use of beta- and gamma-emitting radionuclides.

With emerging PET-imaging technologies identifying early metastatic disease, deployment of ^{223}Ra in the micro metastatic setting could yield even greater clinical benefit given the smaller amount of tumour burden [71]. Furthermore, it is important not to leave treatment with ^{223}Ra for the late phase of disease, to avoid the development of visceral metastases that makes patients ineligible for ^{223}Ra itself. In particular, in the ALSYMPCA trial ^{223}Ra showed to be safe and effective irrespective of prior docetaxel use, and post – ALSYMPCA data documented the safety of chemotherapy administration after ^{223}Ra.

On the other hand, the unique mechanism of action of 223Ra does not potentially overlap with other available treatments, and the drug is suitable for both sequencing and combination studies. Combination therapy may improve outcomes without increasing toxicities [56]. Radium-223 is well tolerated. In the ALSYMPCA trial, there were more adverse events in the placebo group than the radium-223 group. Also, EAP and retreatment trials confirmed how safe and manageable the drug is. However, patients should be evaluated for toxicities using a complete blood count. Complete blood count should be obtained before each cycle of Radium-223 [20], and clinical examination must be performed at each cycle, since it remains the best instrument to evaluate patient response and to drive physicians to further choice.

Future Perspectives

Preliminary results from an ongoing phase I/IIa trial showed that ^{223}Ra in combination with docetaxel in mCRPC is feasible and safe (with lower docetaxel dose at 60 mg/mq every 3 weeks and ^{223}Ra for 5 cycles every 5 weeks) [71]. Currently, several clinical trials are evaluating safety and efficacy of combination treatments of ^{223}Ra with abiraterone acetate (ERA 223, NCT02043678) and enzalutamide (PEACE III, NCT02194842). Another randomized trial compared 50kBq/kg for 12 cycles versus 80 kBq/kg for 6 cycles versus standard dose; this trial completed enrollment, data analysis is ongoing. A potential clinical benefit ^{223}Ra in the hormone-naïve setting is yet to be investigated [43].

Given the mechanism of bone targeting of Radium-223, it is likely that it will have activity against other cancers. There is some interest in extending the treatment indications for Radium-223, with a Phase 1/2 study in patients with osteosarcoma (NCT01833520), a Phase 2 studies in bone predominant metastatic breast cancer (NCT01070485) and metastatic radioiodine-refractory thyroid cancer (NCT02390934).

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