Appropriateness of treatment options in patients with metastatic castration-resistant prostate cancer with a focus on radium-223: outcomes of a Belgian multidisciplinary Consensus Meeting

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SUMMARY

The treatment landscape for metastatic castration-resistant prostate cancer (mCRPC) has changed dramatically with the approval of a variety of therapeutic agents including abiraterone acetate, cabazitaxel, docetaxel, enzalutamide and radium-223 dichloride and the introduction of docetaxel and abiraterone acetate in combination with androgen deprivation therapy in newly diagnosed metastatic prostate cancer. Evidence on the optimal sequence of these therapies is scarce. In practice, the most appropriate treatment (sequence) depends on patient and disease characteristics. This article summarises the recommendations of a multidisciplinary group of Belgian experts in sequencing treatments for patients with mCRPC, with a focus on radium-223 dichloride.

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Keywords: abiraterone acetate, bone metastases, cabazitaxel, docetaxel, enzalutamide, metastatic castration-resistant prostate cancer, patient selection, radium-223, targeted alpha therapy, treatment monitoring, treatment selection, treatment sequence.

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INTRODUCTION

Castration-resistant prostate cancer (CRPC) is defined by biochemical or radiological progression despite castrate testosterone levels (<50 ng/dl or 1.7 nmol/l).[1] Bone metastases are the most frequent metastatic site in metastatic CRPC (mCRPC), present in 60-90% of patients. Many patients will present with complications from their skeletal metastases, usually defined as symptomatic skeletal events (SSEs).[2-4] These SSEs are a major cause of morbidity, pain, decreased quality of life (QoL), patient disability and increased treatment cost. In addition, the development of bone metastases is associated with a rise in mortality.[3] Around 40% of mCRPC patients with bone metastases also have nodal disease, although this seems to have a limited impact on overall survival.[5] Visceral metastases usually develop later in the course of the disease and are associated with bone and nodal metastases in the majority of patients.[6]

Radium-223 dichloride (radium-223) is a targeted alpha therapy that prolongs overall survival (OS) in patients with mCRPC.[2] It attacks the cycle of cancer growth caused by the interplay between prostate cancer (PCa) tumour cells and the bone microenvironment. Approval of radium-223 was based on data from the pivotal phase III ALSYMPCA trial, randomising patients to radium-223 or placebo.[2] Patients on radium-223 had improved OS (14.9 versus 11.3 months; hazard ratio (HR) 0.70, 95% confidence interval (CI): 0.58-0.83, $P<0.001$) irrespective of prior docetaxel use (57% of patients received prior docetaxel) and a significantly longer median time to first SSE (15.6 versus 9.8 months) that was more evident in patients receiving bisphosphonates.[2,7] In addition, the survival advantage was associated with a significantly higher proportion of patients experiencing a meaningful improvement in QoL and a slower decline in QoL over time.[8] Treatment with radium-223 was well-tolerated with a low incidence of myelosuppression.[2] However, one of the main limitations of ALSYMPCA lies in the fact that the other approved OS prolonging agents (abiraterone acetate, enzalutamide, cabazitaxel) were not available for study participants. Nonetheless, according to the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS), radium-223 has the highest clinical benefit of all treatments for mCRPC patients.[9]

Radium-223 was initially indicated for treatment of patients with mCRPC, symptomatic bone metastases and no known visceral metastases. However, the European Medicines Agency (EMA) authorisation and Belgian reimbursement criteria for radium-223 have been changed after the publication of the ERA-223 trial. This phase III study investigated the combination of radium-223 and abiraterone acetate in patients with asymptomatic/mildly symptomatic chemotherapy-naïve mCRPC.[10] In an unplanned ad-hoc analysis an increased risk of fractures in the radium-223 plus abiraterone acetate group compared to the placebo plus abiraterone acetate group was noted, while no significant difference in survival was observed between the 2 groups. Of note, 61% of patients were not receiving bone health agents[10], while the interim analysis of the PEACE III trial suggested that administration of bone health agents to patients receiving an androgen receptor pathway inhibitor (ARPI) combined with radium-223 provides good control of fractures.[11]

The EMA changed the indication of radium-233 in 2018 to "treatment of men with mCRPC, symptomatic bone metastases and no known visceral metastases, in progression after ≥2 prior lines of systemic therapy for mCRPC (other than luteinising hormone-releasing hormone [LHRH] analogues), or ineligible for any available systemic mCRPC treatment".[12] Interestingly, the indication in the label was left unchanged despite a review of the data in the United States, Switzerland, Canada and Japan.

In Belgium, the reimbursement criteria were recently updated: "Radium-223 is reimbursed in mCRPC patients with symptomatic bone metastases and no known visceral metastases in progression after at least 2 prior systemic treatments (other than LHRH analogues) or ineligible to an available systemic mCRPC treatment".[13] The European Association of Urology (EAU) guidelines recommend radium-223 as a first- and second-line (in case of progression following docetaxel) mCRPC treatment option.[1]

Next to radium-223, four other life-prolonging therapies are approved and reimbursed in Belgium for mCRPC treatment: docetaxel and the ARPIs abiraterone acetate and enzalutamide in first- and second-line treatment, and cabazitaxel in second-line treatment after docetaxel.[14-19] This creates an everyday dilemma for physicians when it comes to choosing the most appropriate therapy for individual patients since the evidence regarding treatment sequencing is mostly retrospective.[20,21] In addition, based on several large trials, docetaxel and abiraterone acetate can be administered together with ADT in newly diagnosed metastatic patients, thus creating a new paradigm. Guidelines recommend to base the choice of life-prolonging first- or second-line treatment for mCRPC on (pre-treatment) performance status, symptoms, co-morbidities, location and extent of disease, patient preference, and (in case of first-line treatment) on the previous treatment for metastatic hormone-sensitive PCa (mHSPC).[1,22]

The present paper reports the recommendations of a Belgian multidisciplinary expert panel on the management of mCRPC in routine clinical practice. The aim is to provide guidance on the appropriateness of therapeutic options in different treatment lines with focus on radium-223. In addi-

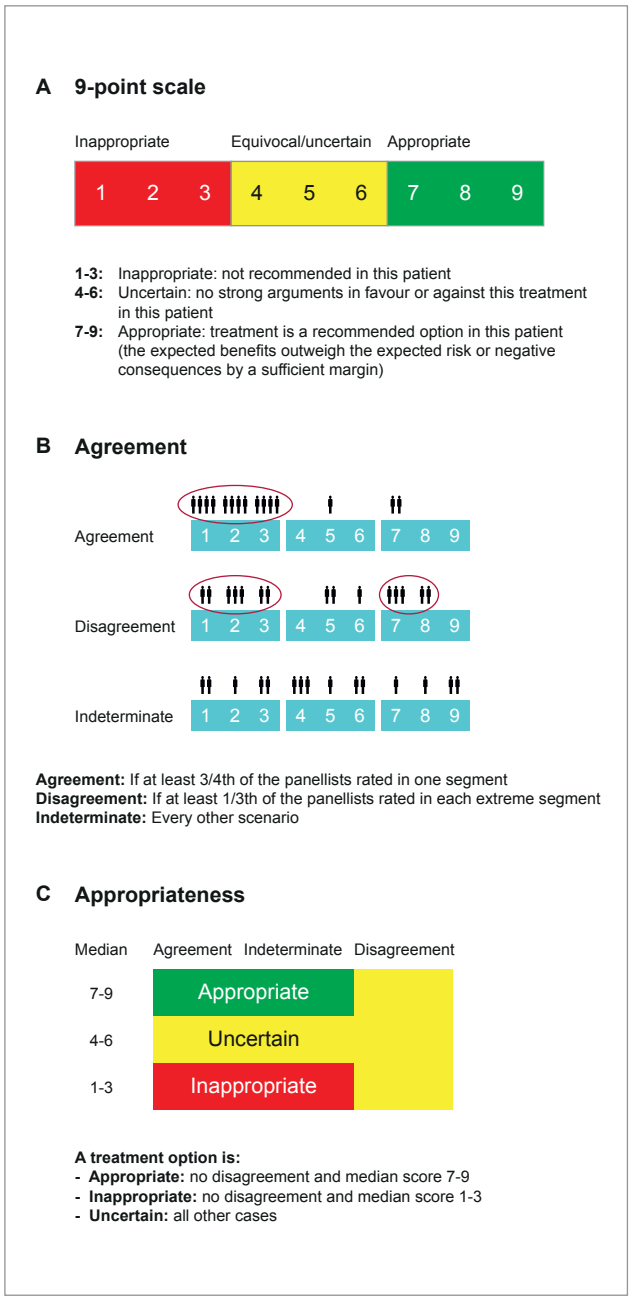


FIGURE 1. Appropriateness scale for individual ratings (A), assessment of agreement between the panellists (as example) (B), and assessment of appropriateness of a treatment option according to the panellists (C).

tion, practical considerations for the use of radium-223 are discussed.

METHODS

The multidisciplinary expert panel consisted of 11 Belgian physicians, including 3 urologists, 5 medical oncologists, 1 radiation oncologist and 2 nuclear medicine physicians. They were asked to rate the appropriateness of treatment options for different mCRPC patient scenarios. The patient scenarios consisted of 5 index cases including 'what if' scenarios in which a patient or disease characteristic changed versus the index case. The following assumptions were made for all patient scenarios: patients have a testosterone level <50 ng/dl while receiving ADT, drugs are prescribed at the registered dose and with the recommended accompanying treatment (e.g. prednisone or supplements), patients have normal values for alkaline phosphatase (ALP), i.e. 23 to 126 U/L, and stage is defined based on standard imaging, i.e. ^{99}mTc-methylene diphosphonate (^{99m}Tc-MDP) bone scan for detection of bone metastases and contrast-enhanced computed tomography (CT) of the chest, abdomen and pelvis for detection of metastatic lymph nodes and visceral metastases. The process consisted of an individual rating round using an online voting tool and a plenary meeting to discuss the results. Panel members were asked to rate according to their clinical judgement. Assessment of appropriateness was based on the rules typically used in RAND-UCLA studies.[23] The RAND-UCLA method is a scientifically validated approach for calculating the level and extent of expert agreement and treatment appropriateness. The appropriateness scale ranged from 1 (extremely inappropriate) to 9 (extremely appropriate) with 5 being equivocal or uncertain *(Figure 1A)*. Based on the extent of agreement and median panel score, the individual ratings were converted to panel statements (appropriate, inappropriate, and uncertain) for each treatment option. Disagreement was defined as at least one third of the panellists rated each extreme segment *(Figure 1B)*. In case of disagreement, the panel outcome was translated as uncertain. In absence of disagreement, a treatment was defined as appropriate in case the median panel score was 7-9, inappropriate in case the median panel score was 1-3, or uncertain in case the median panel score was 4-6 *(Figure 1C)*.

RESULTS AND DISCUSSION

PATIENTS WITH A HISTORY OF RADICAL LOCAL THERAPY PLUS ADT, PROGRESSING TO MCRPC

Details of the different patient scenarios and appropriateness outcomes on mCRPC treatments in this setting are displayed in *Tables 1A, B*.

Index case one concerned a patient who had received radiotherapy (RT) plus ADT for localised PCa and experienced symptomatic progression during first-line mCRPC treatment with abiraterone acetate with a PSA doubling time (PSA-DT) of 9 months *(Table 1A)*.

The expert panel considered both docetaxel and radium-223 appropriate second-line mCRPC treatment options for this patient. As studies have shown little benefit of sequential ARPI treatment, enzalutamide and continuation of abiraterone acetate were considered inappropriate by the panel.[24,25]

TABLE 1A: Appropriateness of mCRPC treatment options in two patient cases with a history of radiotherapy plus androgen deprivation therapy with 'what if' scenarios.

Index case one: second-line mCRPC treatment

RT + ADT → Abiraterone → ?

- Man, 73 years old, GS 3+4 (ISUP G2), PSA 12 ng/ml, cT2b cN1 cM0
- Primary RT + 3 years ADT
  - PSA nadir of 0.5 ng/ml at 6 months
- 28 months after start of ADT:
  - PSA 4 ng/ml (confirmed rise)
  - Testosterone level <35 ng/dl
  - 2 bone metastases on bone scintigraphy confirmed by CT scan, without other lesions
  - No symptoms
  - Normal ALP
- Starts abiraterone + prednisone + denosumab + calcium and Vitamin D
  - PSA nadir of 0.4 ng/ml
- 16 months after start of abiraterone:
  - PSA 4 ng/ml (confirmed rise >2 ng/ml)
  - PSA-DT 9 months
  - 8 bone metastases with 1 symptomatic lesion on Th1 (paracetamol 1g 3x/day BPI score 3)
  - No visceral metastases or lymph node metastases >2 cm
  - ALP 120 U/L (normal range 35-105 U/L)
  - Rest of bloodwork normal
  - ECOG 1

		Treatment			
		Abiraterone continued	**Docetaxel**	**Enzalutamide**	**Radium-223**
Index case one					
A	What if PSA-DT <6 months				
B	What if number of bone metastases <6				

Grey boxes in schematic overview indicate castration-resistant state. red: inappropriate; yellow: uncertain; green: appropriate

ADT: androgen deprivation therapy; ALP: alkaline phosphatase; ARPI: androgen receptor pathway inhibitor; BPI: Brief Pain Inventory; CT: computed tomography; ECOG PS: Eastern Cooperative Oncology Group Performance Status; GS: Gleason score; ISUP: International Society of Urological Pathologists; mCRPC: metastatic castration-resistant prostate cancer; PSA: prostate-specific antigen; PSA-DT: prostate-specific antigen doubling time; RT: radiation therapy.

PLATO, a phase IV randomised, double-blind, placebo-controlled trial, investigated the efficacy of abiraterone acetate alone or combined with enzalutamide in mCRPC patients with rising PSA during enzalutamide treatment.[24] No significant differences between both groups were observed in median progression-free survival and secondary endpoints, and the clinical benefit of abiraterone acetate following enzalutamide was very limited. In addition, a multi-centre, phase II study randomised 202 treatment-naïve mCRPC patients to abiraterone acetate or enzalutamide with a cross-over at PSA progression.[25] The results showed limited benefits from the sequential use of ARPIs.

Radium-223 was considered uncertain in case of rapidly progressing disease (PSA-DT <6 months), which may be explained by an increased risk of visceral metastases or the inability to administer 6 cycles of radium-223. Docetaxel was considered uncertain in case of fewer bone metastases (<6), while the number of bone metastases did not impact the appropriateness of radium-223.

When looking specifically at the appropriate treatment options of index case one, namely docetaxel and radium-223, it should be noted that in the Belgian situation, the patient should be considered ineligible to docetaxel in order to be reimbursed for radium-223 in this setting, e.g. a PSA-DT >6 months or when he is too frail to receive docetaxel.[13]

Index case two described a patient who had received RT plus

TABLE 1B: Appropriateness of mCRPC treatment options in two patient cases with a history of radiotherapy plus androgen deprivation therapy with 'what if' scenarios.

Index case two: third-line mCRPC treatment

RT + ADT → Abiraterone → Docetaxel → ?

- Man 68 years old, GS 3+4 (ISUP G2), PSA 12 ng/ml, cT3a cN1 cM0
- Primary RT + 3 years ADT
  - PSA nadir of 0.5 ng/ml at 6 months
- 28 months after start of ADT:
  - PSA nadir of 0.5 ng/ml at 6 months
  - PSA 4 ng/ml (confirmed rise)
  - Testosterone level <35 ng/dl
  - 2 bone metastases on bone scintigraphy confirmed by CT scan, without other lesions
  - No symptoms
  - Normal ALP
- Starts abiraterone + prednisone + denosumab + calcium and Vitamin D
  - PSA nadir of 0.5 ng/ml at 6 months
- 16 months after start of abiraterone:
  - PSA 4 ng/ml (confirmed rise)
  - PSA-DT 4 months
  - 8 bone metastases with 1 symptomatic lesion on Th1 (paracetamol 1g 3x per day, BPI score 3)
  - No visceral metastases or lymph node metastases >2 cm
  - ALP 120 U/L (normal range 35-105 U/L)
  - Rest of bloodwork normal
  - ECOG 1
- Starts docetaxel for 9 cycles
  - PSA nadir of 0.2 ng/ml and stable disease at the end of treatment
- PSA progression and progression of bone metastases 6 months after docetaxel discontinuation
  - No visceral metastases or lymph node metastases >2 cm

		Treatment			
		ARPI	**Cabazitaxel**	**Docetaxel rechallenge**	**Radium-223**
Index case two					
A	What if the patient progresses during the docetaxel treatment (PSA and bone metastases)				

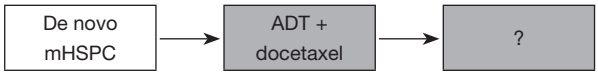
Grey boxes in schematic overview indicate castration-resistant state. red: inappropriate; yellow: uncertain; green: appropriate

ADT: androgen deprivation therapy; ALP: alkaline phosphatase; ARPI: androgen receptor pathway inhibitor; BPI: Brief Pain Inventory; CT: computed tomography; ECOG PS: Eastern Cooperative Oncology Group Performance Status; GS: Gleason score; ISUP: International Society of Urological Pathologists; mCRPC: metastatic castration-resistant prostate cancer; PSA: prostate-specific antigen; PSA-DT: prostate-specific antigen doubling time; RT: radiation therapy.

adjuvant ADT for locally advanced PCa, was treated with first-line abiraterone acetate for mCRPC and progressed after second-line docetaxel *(Table 1B)*. The expert panel considered cabazitaxel and radium-223 appropriate third-line mCRPC treatment options for this patient. Although both agents are reimbursed in this setting in Belgium[13], it was discussed that in clinical practice these are prescribed for two different patient profiles: while radium-223 should be considered for patients with bone-dominant disease, cabazitaxel holds a place for men with rapidly progressing disease. Docetaxel rechallenge and ARPIs were considered uncertain treatment options. If the patient would have progressed during, instead of after, second-line docetaxel treatment, the panel considered cabazitaxel an appropriate third-line treatment option, ARPIs and radium-223 uncertain treatment options and docetaxel an inappropriate option. There was consensus among the panellists that every patient should be given the possibility to maximise the number of treatment

TABLE 2A: Appropriateness of mCRPC treatment options in three patient cases with *de novo* mHSPC progressing to mCRPC with 'what if' scenarios.

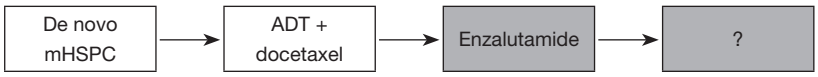
Index case three: first-line mCRPC treatment



- Man, 68 years old, GS 4+4 (ISUP G4), PSA 12 ng/ml, cT3a cN1 cM1b (4 bone metastases with 1 beyond pelvis/spine on bone scintigraphy), asymptomatic
- Primary treatment: ADT + 6 cycles docetaxel
  - PSA nadir of 0.5 ng/ml at 6 months
- 24 months after start of ADT + docetaxel:
  - PSA 4 ng/ml (confirmed rise)
  - PSA-DT 6 months
  - 8 bone metastases with 1 symptomatic lesion on Th1 (paracetamol 1g 3x/day, BPI score 3)
  - No visceral metastases or lymph node metastases >2 cm
  - ALP-levels 120 U/L (normal range 35-105 U/L)
  - Rest of bloodwork normal
  - Testosterone level <35 ng/dl
  - ECOG 1

		Treatment			
		ARPI	**Cabazitaxel**	**Docetaxel**	**Radium-223**
Index case three					
A	What if BPI score >3 at progression				

Index case four: second-line mCRPC treatment

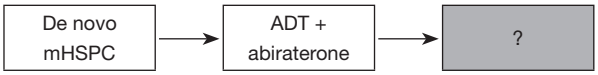


- Man, 68 years old, GS 4+4 (ISUP G4), PSA 12 ng/ml, cT3a cN1 cM1b (4 bone metastases with 1 beyond pelvis/spine on bone scintigraphy), asymptomatic
- Primary treatment: ADT + 6 cycles docetaxel
  - PSA nadir of 0.5 ng/ml at 6 months
- 24 months after start of ADT + docetaxel
  - PSA 4 ng/ml (confirmed rise)
  - PSA-DT 6 months
  - 4 bone metastases with 1 symptomatic lesion on Th1 (paracetamol 1g 3x/day, BPI score 3)
  - No visceral metastases or lymph node metastases >2 cm
  - ALP-levels 120 U/L (normal range 35-105 U/L)
  - Rest of bloodwork normal
  - Testosterone level <35 ng/dl
  - ECOG PS 1
- Starts enzalutamide. 18 months after start of enzalutamide:
  - Increasing PSA with PSA-DT >6 months
  - Progressive bone metastases: 8 bone metastases with 1 symptomatic lesion on Th1 (paracetamol 1g 3x/day, max BPI score 3)
  - No visceral metastases or lymph node metastases >2 cm

		Treatment				
		Abiraterone	**Cabazitaxel**	**Docetaxel**	**Enzalutamide continued**	**Radium-223**
Index case four						
A	What if the response to enzalutamide is less than 3 months					
B	What if the response to enzalutamide is 18 months, and PSA-DT is 3 months					

TABLE 2B: Appropriateness of mCRPC treatment options in three patient cases with *de novo* mHSPC progressing to mCRPC with 'what if' scenarios.

Index case five: first-line mCRPC treatment



- Man, 68 years old, GS 4+4 (ISUP G4), PSA 12 ng/ml, cT3a cN1 cM1b (4 bone metastases with 1 beyond pelvis/spine on bone scintigraphy), asymptomatic
- Primary treatment: ADT + abiraterone + prednisone
  - PSA nadir of 0.4 ng/ml at 6 months
- 24 months after start of ADT + abiraterone:
  - PSA 4 ng/ml (confirmed rise)
  - PSA-DT 6 months
  - 8 bone metastases with 1 symptomatic lesion on Th1 (paracetamol 1g 3x/day, BPI score 3)
  - No visceral metastases or lymph node metastases >2 cm
  - ALP-levels 120 U/L (normal range 35-105 U/L)
  - Rest of bloodwork normal
  - Testosterone level <35 ng/dl
  - ECOG PS 1

		Treatment			
		Abiraterone continued	**Docetaxel**	**Enzalutamide**	**Radium-223**
Index case five					
A	What if PSA-DT is 11 months				

Grey boxes in schematic overview indicate castration-resistant state. red: inappropriate; blue: uncertain; green: appropriate

ADT: androgen deprivation therapy; ALP: alkaline phosphatase; ARPI: androgen receptor pathway inhibitor; BPI: Brief Pain Inventory; ECOG PS: Eastern Cooperative Oncology Group Performance Status; GS: Gleason score; ISUP: International Society of Urological Pathologists; mCRPC: metastatic castration-resistant prostate cancer; PSA: prostate-specific antigen; PSA-DT: prostate-specific antigen doubling time.

lines. This is important as a current treatment choice may impact future treatment options.

DE NOVO MHSPC PATIENTS PROGRESSING TO MCRPC

The different patient scenarios and appropriateness outcomes on mCRPC treatments for this setting are shown in *Tables 2A, B*. The expert panel agreed that if a patient has received ADT plus docetaxel or ADT plus abiraterone acetate for mHSPC, this should be counted as one line of systemic therapy referring to the Belgium reimbursement criteria.

Index case three concerned a patient who presented with bone metastases at diagnosis and was treated with ADT plus 6 cycles docetaxel (*Table 2A*). After 24 months, he became castration-resistant with a brief pain inventory (BPI) score of 3. Overall, the expert panel considered first-line mCRPC treatment (or second-line systemic treatment) with an ARPI appropriate while docetaxel rechallenge was considered uncertain. This is in line with a retrospective analysis of the GETUG-15 trial, suggesting that abiraterone acetate and enzalutamide still have anti-cancer activity in mCRPC patients who have received ADT plus docetaxel in mHSPC setting. Docetaxel rechallenge seems to have a rather limited activity in this setting.[26] The experts also considered radium-223 an appropriate first-line mCRPC treatment option while cabazitaxel was considered uncertain. The treatment recommendations by the expert panel were independent of the level of pain at progression (BPI score >3; *Table 2A*).

When looking at the appropriate treatment options of index case three in the Belgian situation, an ARPI is not reimbursed if the patient is considered eligible for docetaxel.[13] Furthermore, radium-223 is only reimbursed if the patient is considered ineligible for any available systemic treatment.

Index case four concerned a patient with presence of bone metastases at diagnosis who was treated with ADT plus 6 cycles docetaxel (*Table 2A*). He progressed to mCRPC after 24

months, was treated with enzalutamide but progressed after 18 months with a PSA-DT >6 months. The expert panel considered radium-223 and cabazitaxel appropriate second-line mCRPC treatment options. Treatment with an ARPI was considered inappropriate and docetaxel uncertain for reasons discussed earlier.[24-26] The panel recommendations were also in favour of appropriateness of radium-223 and cabazitaxel in case of a shorter response to enzalutamide (3 months) or a shorter PSA-DT (3 months).

Focussing on the appropriate treatment options of index case four, namely cabazitaxel and radium-223, it should be noted that radium-223 but not cabazitaxel would be reimbursed in Belgium.[13]

Index case five concerned a patient with presence of bone metastases at diagnosis treated with ADT plus abiraterone acetate *(Table 2B)*. He became castration-resistant after 24 months with a PSA-DT of 6 months. The expert panel considered both docetaxel and radium-223 appropriate first-line mCRPC treatment options for this patient. Both enzalutamide and continuation of abiraterone acetate were considered inappropriate by the panel as studies have shown little benefit of sequential ARPI treatment.[24,25] Treatment recommendations for this case were similar if the patient progressed slower (PSA-DT 11 months; *Table 2B*).

When looking specifically at the appropriate treatment options of index case five, namely docetaxel and radium-223, it should be noted that in the Belgian situation radium-223 is only reimbursed in this setting if the patient is considered ineligible for docetaxel, e.g. a PSA-DT >6 months or when he is unwilling to receive docetaxel.[13]

PRACTICAL CONSIDERATIONS FOR THE USE OF RADIUM-223

INITIATION OF RADIUM-223

Selection of patients suitable for radium-223

In general, mCRPC treatment should be tailored to the patient and discussed by a multidisciplinary team in order to achieve the most appropriate and broadest range of treatment options. Close interaction between different disciplines and departments, more particularly nuclear medicine, radiation oncology, medical oncology and urology services, facilitates the identification of patients eligible for radium-223 treatment.[27] In addition, patient preferences and expectations should be taken into account.

According to the expert panel, the best window of opportunity for radium-223 includes patients with bone predominant disease (≥2 bone metastases on bone scan) before any development of visceral disease and/or malignant lymphadenopathy >3 cm in their minor axis.

In addition, there was consensus that patients should be able to receive 6 cycles of radium-223 to obtain the highest survival benefit; starting radium-223 if it is likely that the patient will not be able to receive 6 cycles was generally considered inappropriate. Prospective and retrospective studies (ALSYMPCA, EAP, BELFIGO) have shown that earlier use of radium-223 in mCRPC patients increases the likelihood of completing therapy and better outcomes.[28-30] Indeed, receiving 5-6 cycles of radium-223 was associated with longer overall survival compared to 1-4 cycles.[28,29] Patients who discontinued radium-223 after 1-4 cycles most often did because of disease progression and were more likely to have more advanced or more rapidly progressing mCRPC at the start. Since patients with more advanced or more rapidly progressing disease seem to be less likely to complete the recommended 5-6 cycles, radium-223 should be considered as early as appropriate in the treatment course of patients with mCRPC and bone metastases.[31]

Baseline measurements

Prior to the start of radium-223 treatment, bone metastasis osteoblastic activity must be confirmed by functional bone imaging and data concerning symptoms should be collected.[32] Haematological evaluation must be performed at baseline with the absolute neutrophil count measuring ≥1.5 x 10^9/l, the platelet count ≥100 x 10^9/l and haemoglobin ≥10.0 g/dl.[12]

Bone health

Guidelines recommend to offer bone protective agents to mCRPC patients with skeletal metastases to prevent osseous complications.[1,22] When prescribing either denosumab or bisphosphonates, calcium and vitamin D supplementation together with preventive dental care should be offered as well. Caution is advised in patients with dental problems due to an increased risk of osteonecrosis of the jaw.[1,22] Painful bone metastases should be treated early on with palliative measures such as external beam radiation therapy (EBRT) and adequate use of analgesics. Radium-223 can be safely used in combination with EBRT in case of painful focal bone metastases that require rapid pain palliation and with bone protective agents (bisphosphonates and denosumab) to prevent osseous complications.[2]

Contraindications

Following the interim analysis of the phase III ERA-223 trial, combination therapy with radium-223 and abiraterone is currently contra-indicated.[12]

MONITORING DURING RADIUM-223 TREATMENT

Haematological evaluation of patients must be performed prior to every injection (or cycle) of radium-223 with the abso-

KEY MESSAGES FOR CLINICAL PRACTICE

1. Every patient with metastatic PCa should be given the possibility to receive as many life-prolonging treatment options as possible.
2. Radium-223 is an anti-cancer drug associated with overall survival benefit and a delayed time to the occurrence of SSEs, is well-tolerated and is administered for a determined period. The overall survival benefit is comparable to the survival benefit of other agents in the mCRPC setting.
3. Radium-223 is indicated for mCRPC patients with symptomatic bone metastases and no known visceral metastases, in progression after ≥2 prior lines of systemic therapy for mCRPC, or ineligible for any available systemic mCRPC treatment. Because radium-223 should be administered before progression to visceral metastases and/or lymph nodes >3 cm, it should be given as early in the disease course as possible. Both ARPIs and docetaxel can still be given after radium-223 treatment.
4. Completion of 6 cycles of radium-223 is of paramount importance in order to achieve the best clinical benefit related with this treatment. Heavily pre-treated patients are less likely to complete 6 cycles of radium-223.
5. mCRPC patients with bone metastases should receive bone health agents, irrespective of the life-prolonging treatment.

lute neutrophil count ≥1.0 x 10^9/l and the platelet count ≥50 x 10^9/l.[12] The panellists agreed that during radium-223 treatment a CT of chest, abdomen and pelvis together with blood tests could in general be performed every 3 months, taking into account that the precise timing of these exams is usually individualised. According to the expert panel, standard biomarkers in the blood (e.g. PSA, ALP and lactate dehydrogenase [LDH]) may increase during radium-223 treatment. Therefore, patients should be informed that a PSA rise during radium-223 treatment does not imply a lack of efficacy of radium-223. In addition, it has been shown in the ALSYMPCA trial that dynamic changes in ALP and LDH during radium-223 treatment might be useful for monitoring, but do not serve as surrogates for survival.[33] The EAU guidelines state that PSA alone is not reliable enough for monitoring disease activity in advanced CRPC, since visceral metastases may develop in men without rising PSA.[1] According to the PCWG3 (Prostate Cancer Working Group 3) on-treatment evaluations should look at the general clinical status of the patient, including physical examinations, symptom assessments, and laboratory studies.[34] The PCWG3 also recommends that a combination of bone scintigraphy and CT scans, PSA measurements and an assessment of the clinical benefit should be performed in assessing men with mCRPC. In addition, at the 2017 Advanced Prostate Cancer Consensus Conference (APCCC) 75% of the experts suggested bone scintigraphy and CT scans for monitoring mCRPC patients treated with radium-223.[35] In general, in line with the current EAU guidelines, the panellists agreed to only start a subsequent treatment if the patient progresses, i.e. has two of the following factors: PSA, radiological or clinical progression.[1]

FOLLOW-UP AFTER RADIUM-223

There was consensus among the panellists to perform a bone scan at least one month after the last radium-223 injection. Once the last cycle is terminated, the majority of panellists recommend to monitor the patient every three months (including ALP, LDH, PSA, full blood count, CT and bone scan) until a new treatment is initiated. If there is a clinical indication of progressive disease, examinations should be performed earlier.

With regard to the next line of treatment, a pre-specified subgroup analysis from ALSYMPCA showed that docetaxel following radium-223 is still feasible and well-tolerated in patients with mCRPC.[36] An interim analysis of REASSURE, a global prospective trial, confirmed the safety of radium-223 in routine clinical practice and showed again that it is safe to use docetaxel after radium-223.[37] The panellists agreed that both chemotherapy and ARPIs can still be safely administered after radium-223 treatment. Overall, they concluded that every patient with metastatic PCa should be given the possibility to receive as many life-prolonging treatment options as possible.

CONCLUSIONS

No clear guidelines exist on how to sequence the different therapeutic options for patients with mCRPC. These pa-

tients should be discussed by a multidisciplinary team in order to achieve the most appropriate treatment. As stated in the EAU guidelines, the choice of first- or second-line treatment should be based on (pre-treatment) performance status, symptoms, co-morbidities, location and extent of disease, patient preference, and (in case of first-line treatment) on the previous treatment for mHSPC. Every patient with metastatic PCa should be given the possibility to receive as many life-prolonging treatment options as possible. Since radium-223 should be administered before progression to visceral metastases and/or lymph nodes >3 cm, it should be given as early as appropriate in the disease course.

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