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Castration-resistant prostate cancer: current status of therapy with Radium-223 associated with anti-androgens (enzalutamide and abiraterone) - a systematic literature review

Câncer de próstata resistente à castração: estado atual do tratamento com Rádio-223 associado com anti-androgênios (enzalutamia e abiraterona) - uma revisão sistemática da literatura

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ABSTRACT: BACKGROUND. Recently, a new range of therapeutic options became available for men with advanced castration-resistant prostate cancer (CRPC), including antiandrogens (abiraterone acetate, enzalutamide), taxanes (docetaxel, cabazitaxel) and a radionuclide (radium-223). The development of abiraterone and enzalutamide, as well as the advent of Ra-223, led to significant improvements in CRPC clinical outcomes. However, there are currently few data regarding the optimal sequence or concomitant use of Ra-223 with these most recently approved endocrine agents. OBJECTIVE. To systematically identify and analyse articles that brings information about the concomitant or sequential use of radium-223 (Ra-223) associated with antiandrogenic drugs (abiraterone or enzalutamide) in the therapy of CRPC. METHODS. PubMed (mesh and free terms), Scopus and Clinical Trials were searched to identify published articles about the sequential or association use of radium-223. RESULTS. A total of 484 references were identified by the literature search and after exclusion and inclusion criteria 36 were screened. 4 publications that met the selection criteria were included in this review; of these 2 were cost-effectiveness studies and 2, case series. Overall, safety profiles in relation to therapy with Ra-223 were similar regardless of use or not of enzalutamide or abiraterone. Response were higher for the combinations of Ra-223 with abiraterone while with enzalutamide no improvements were found. The drugs do not seem to have great differences in costs and there is still no consensus on the most cost-effective treatment in the short and long term. CONCLUSION. Further studies are necessary to evaluate the best treatment regimen (concurrent or sequential) of Ra-223 and new antiandrogens. By now, data show that the best association of use may be with abiraterone. There are ongoing clinical trials that aim to precisely study the use of these drugs together, therefore in the next few years this situation tends to change.

Keywords: Radioisotopes; Prostatic neoplasms, castration-resistant; Androgen antagonists.

RESUMO: INTRODUÇÃO. Recentemente, uma nova gama de opções terapêuticas tornou-se disponível para homens com câncer de próstata resistente à castração (CPRC), incluindo anti-androgênios (acetato de abiraterona, enzalutamida), taxanos (docetaxel, cabazitaxel) e um radionuclídeo (rádio-223). O desenvolvimento de abiraterona e enzalutamida, bem como o

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advento de Ra-223, levou a melhorias significativas nos resultados clínicos do CPRC. No entanto, existem atualmente poucos dados sobre a sequência ideal ou uso concomitante de Ra-223 com estes agentes endócrinos recentemente aprovados. OBJETIVO. Identificar e analisar sistematicamente os artigos que trazem informações sobre o uso concomitante ou sequencial de rádio-223 (Ra-223) associado com drogas antiandrogênicas (abiraterona ou enzalutamida) na terapia de CPRC. MÉTODOS. PubMed (mesh e termos livres), Scopus e ensaios clínicos foram utilizados para identificar artigos publicados sobre o uso sequencial ou associação de rádio-223 com anti-androgênios(enzalutamida e abiraterona). RESULTADOS. Um total de 484 referências foram identificadas pela pesquisa bibliográfica e, após aplicar critérios de exclusão e inclusão, 36 foram selecionadas. Quatro publicações que atenderam aos critérios de seleção foram incluídas nesta revisão; destas, 2 são estudos de custo-eficácia e 2 são séries de casos. No geral, os perfis de segurança em relação à terapia com Ra-223 foram semelhantes independentemente do uso ou não de enzalutamida ou de abiraterona. As taxas de resposta ao tratamento indicaram benefício na combinação de Ra-223 com abiraterona, mas a combinação com enzalutamida não indicou evidências positivas. As drogas não parecem ter grandes diferenças em relação à despesa total e ainda não há um consenso sobre o tratamento mais viável economicamente no curto e longo prazo. CONCLUSÃO. Mais estudos são necessários para avaliar a melhor eficácia do tratamento concomitante ou sequencial de Ra-223 com os novos anti-androgênios. Até agora, os dados mostram que a melhor associação pode ser com abiraterona. Há ensaios clínicos em curso que visam estudar precisamente o uso desses medicamentos em conjunto, portanto, nos próximos anos, essa situação tende a mudar.

Descritores: Radioisótopos; Neoplasias de próstata resistentes à castração; Antagonistas de androgênios

INTRODUCTION

New therapies for advanced prostate cancer have been introduced in recent years, but it is not clear if the association or sequential use of different drugs may offer incremental response in this context.

It is estimated that in the United States prostate cancer is responsible for 26% of new cancer cases in men and contributes with 9% of all cancer deaths. Furthermore, in Brazil this disease is responsible for 22% of new cancer cases[1,2]. Clinical presentation varies, ranging from early and localized disease to advanced, metastatic disease. Patients with metastatic prostate cancer are treated with classic anti-androgenic therapy aiming chemical castration in order to remove the most important stimulus for prostate cells proliferation. However, after 1 or 2 years of treatment it becomes ineffective, culminating in the clinical entity known as castration-resistant prostate cancer (CRPC)[3].

The first drug approved for the management of CRPC was mitoxantrone, based on studies that had shown palliative benefits, but not translated into improved survival[4]. Next, docetaxel demonstrated benefit in overall survival (average 2-3 months), and until 2010 no other substance had shown differences in this aspect[5]. However, most of the patients treated with docetaxel develop resistance to treatment and their disease progresses. Recently, a new range of therapeutic options as cabazitaxel, abiraterone acetate, enzalutamide, sipuleucel-T, and Ra-223 became available, generating hope to change this paradigm[6].

With a better knowledge about the pathophysiology of CRPC, it was shown that the progression of the disease is still dependent on androgens, possibly due to structural and functional changes in the androgen receptor and its signaling pathway. It was concluded, therefore, that a more effective hormonal control to reduce plasma testosterone levels could be beneficial. The discovered evidence of the crucial role of androgen receptor led to the development of new anti-androgens such as enzalutamide and abiraterone acetate. The abiraterone acetate is a potent, irreversible inhibitor of cytochrome P450 17A1, which suppresses androgen synthesis and can act as an antagonist of the androgen receptor[7]. Similarly, enzalutamide is an antagonist of the androgen receptor that can block the binding of testosterone, preventing nuclear translocation of the androgen receptor, binding to DNA and recruiting coactivators[8].

Along with the development of these drugs, new therapeutic agents that act on bone metastasis were also investigated. In advanced stages of this malignancy, bone metastasis are developed in 90% of patients with metastatic disease and have a significant impact on quality of life not only because of bone pain, but also due to the risks of bone events. A better understanding of the mechanisms associated with bone disease secondary to prostate cancer and the relation between tumor cells and the bone microenvironment were part of the basic knowledge that allowed the development of effective drugs for this situation, including the radium-223. Radium-223 (Ra-223) is a calcium mimetic that preferentially binds to areas of newly formed bone in prostate bone metastases, being the first alpha radiation emitting radionuclide that has been developed for clinical use. The high energy transferred by the alpha particle causes irreversible double breaks in the DNA of tumor cells. The particles' large size, when compared with other forms of radiation, results in a narrower range of action and highly localized tissue destruction, contributing, in theory, to mitigate bone marrow failure (BMF)[9].

The development of abiraterone and enzalutamide, as well as the advent of Ra-223, led to significant improvements in CRPC clinical outcomes. However, there

are currently few data regarding the optimal sequence or concomitant use of Ra-223 with the most recently approved endocrine agents.

OBJECTIVES

This systematic review aims to gather evidence about the concomitant use of Ra-223 associated with antiandrogenic drugs (abiraterone or enzalutamide) in the therapy of CRPC, focusing on the following endpoints: overall survival (OS), the occurrence of bone events (BE), survival free of skeletal related events (SRE), cost-effectiveness (CE), pain reduction (PR), toxicity (T) and tolerance to treatment (TT).

METHODS

Evidence acquisition

For our research, the following databases were searched in April, 2016: MEDLINE (MeSH and free terms), Scopus and Clinical Trials. During the studies selection, the evaluation of titles and summaries (abstracts) identified in the initial search was conducted by two researchers independently, with any disagreements resolved by consensus. When the title and summary were not enlightening, the full article was analyzed.

The selected studies were categorized (clinical trials, case series, cost-effectiveness studies), and the information about the study design, study population, methodology, results and major conclusions recorded. The results were organized in tables and analyzed critically, seeking explanations for the different or conflicting results.

Study selection

In MEDLINE, the following keywords and strategies were used: ("Prostatic Neoplasms, Castration-Resistant" [mesh] OR "Prostatic Neoplasms" [mesh]) AND ("radium Ra 223 dichloride" [Supplementary Concept] OR "Radium / therapy use "[mesh] OR" Radium "[mesh]) AND (" Androgen Antagonists "[mesh] OR" Androgen Receptor Antagonists "[mesh] OR" MDV 3100 "[Supplementary Concept] OR" abiraterone "[Supplementary Concept]). Another search was made for the free terms radium 223 AND (prostatic neoplasms OR prostate cancer) AND (abiraterone OR enzalutamide OR MDV 3100 OR androgen antagonists OR androgen receptor antagonists), aiming to identify studies not yet indexed by descriptors.

In Scopus, the following keywords were used: alpharadin OR radium 223 OR xofigo AND prostate cancer AND abiraterone OR enzalutamide OR antiandrogens.

In the Clinical Trials platform there was made a survey of clinical trials records with Ra-223 that involved the sequential or combined use of enzalutamide or abiraterone.

Inclusion and exclusion criteria

Articles identified by the initial search strategy were evaluated independently by two authors, according to the following inclusion criteria: (1) patients with CRPC; (2) use of Ra-223 associated or in sequential use with enzalutamide or abiraterone; (3) Description of clinical outcomes in terms of overall survival, pain reduction, cost-effectiveness, skeletal event-free, survival or toxicity; (4) articles available for free or through subscriptions made by the University of São Paulo; (5) Article wrote in the period from 2013 to 2016. There were excluded from the analysis (1) review articles; (2) studies without clear description of the used medications and doses; (3) absence of clinical outcome description; (4) articles written in language other than English.

RESULTS

The search for mesh terms in MEDLINE resulted in 23 articles; review articles were excluded, remaining 5 articles. In the analysis, none of them were selected due to the lack of information about the associated or sequential use of abiraterone or enzalutamide with Ra-223.

The search for free terms in MEDLINE resulted in 115 articles, after excluding review articles and articles that were written out of the period from 2013 to 2016, 24 articles were obtained and screened. From these, 8 were guidelines or recommendations of use and were therefore excluded, 12 were excluded due to the lack of information about the associated or sequential use of abiraterone or enzalutamide with Ra-223. 4 articles fitted in the criteria and were included (Table 1).

In Scopus, the search resulted in 344 articles and after excluding review articles, articles written in language other than English and out of the period of selection, 65 articles were obtained and screened. After excluding duplicates with MEDLINE and searching for association or sequential use, 3 congress posters were found but not included due to the lower reliability of the poster format (Figure 1).

In Clinical Trials platform, seven studies that fitted the criterias were found, but none with results currently available, so they were excluded from the analysis.

Table 1. Summary of included articles

Authors	Publication year	Research Design	Casuistry (n)	Comparison groups, intervention (treatment and doses)	Analyzed outcomes (toxicity, response or cost-effectiveness)	Major Results
Etchebehere EC, et al.[10]	2016	Case series	110	Before vs After use of radium-223 (50 kBq/kg, 1x for month, up to 6 cycles)	OS, PFD, BEFS, BMF, Hb, PSA, PA, ECOG, CT, EBRT, RaTot, AB, EZ	The associated use with abiraterone, but not enzalutamide seems to have a beneficial effect.
Dan TD, et al.[13]	2015	Case series	25	radium-223 (50kBq/kg, 1x month, for 6 cycles) alone vs radium-223 + EZ vs radium-223 + AB	Complete blood counts, Hb e PSA	Concomitant use of radium-223 with both anti-androgens have similar toxicity to its use alone.
Guirgis HM.[11]	2015	Cost-effectiveness study	-	radium-223 vs EZ vs AB	Cost for LYG,cost per likelihood of survival and relative values	AB, EZ, radium-223, were overpriced for their results
Bui CN, et al.[12]	2016	Cost-effectiveness study	-	EZ vs other drugs (including radium-223 and AB) in patients who have not received chemotherapy	IABI (PPPY, PPPM, PMPM)	Lower cost of administration, monitoring, and AE associated with the use of EZ compared with other treatment options.

Legend: overall survival (OS), progression free disease (PFD), bone events free survival (BEFS), bone marrow failure (BMF), hemoglobin (Hb), prostate specific antigen (PSA), alkaline phosphatase (AP), Eastern Cooperative Oncology Group (ECOG) status, chemotherapy (CT), external beam radiation therapy (EBRT), progression free survival (PFS), number of total Ra-223 cycles (RaTot), abiraterone (AB), enzalutamide (EZ), life year gained (LYG), incremental aggregate budget impact (IABI) per patient per year (PPPY), per patient per month (PPPM), and per member per month (PMPM).

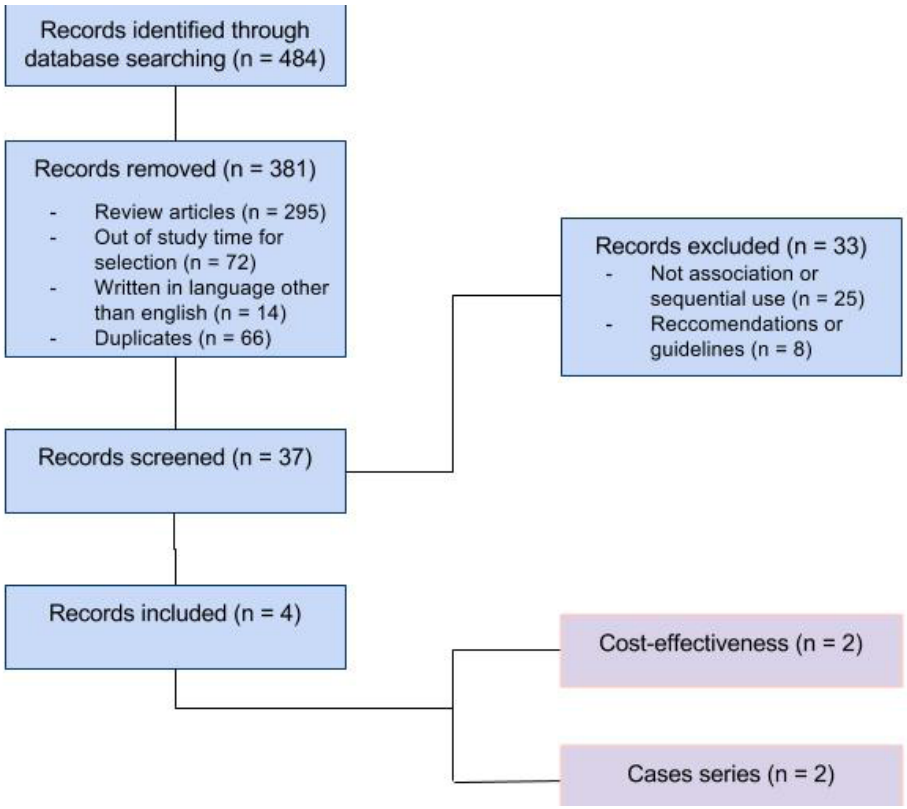

Figure 1. Summary of found and included articles

Main results

In a retrospective review of 110 patients with metastatic CRPC treated with Ra-223, it was reported that 55 (50%) patients received anti-androgens prior to and 49 (45%) during or after Ra-223 therapy (Table 2)[10]. Abiraterone was used in 69 patients and enzalutamide in 30 cases. Interestingly, 36% of patients undergoing Ra-223 therapy had visceral or lymph node metastases. Bone marrow failure was the major cause of death (88% of the cases), and had a significant correlation with the association of Ra-223 and external beam radiation, but not with the association of Ra-223 plus chemotherapy. In multivariate analysis total number of radium cycles (RaTot) and association of Ra-223 with abiraterone were the only ones who remained associated with overall survival ($p < 0.001$ and $p = 0.019$, respectively), progression-free survival ($p < 0.001$ and $p = 0.041$) and survival free of bony events ($p < 0.001$ and p 0.019) (Table 3). Additionally, RaTot ($p = 0.027$) and EBRT ($p = 0.013$) remained significantly associated with BMF. There were clear benefit in OS ($p \leq 0.008$), bone events free survival ($p \leq 0.020$), and PFS ($p \leq 0.003$) with concomitant or after use of Ra-223 with abiraterone. In this population, patients receiving both drugs had a 77% reduction in the risk of death, 88% in the risk of bone related event and a 68% reduction in the risk of progression. Apparently, the study does not mention if the use of abiraterone before the Ra-223 is associated with a reduction in the evaluated parameters. The use of enzalutamide did not result in benefits in those patients in any of the endpoints evaluated[10].

Table 2. Results from study' s variable analysis

Variables	OS		PFS		BMT		BEFS	
	HR 95% CI	p-value	HR 95% CI	p-value	HR 95% CI	p-value	HR 95% CI	p-value
Univariate analysis								
Abiraterone during/ after	0.23	0.002	0.32	<0.0001	N/E	N/E	0.22	<0.001
Ra-223	0.09		0.18				0.09 -	
Yes vs No	0.58		0.55				0.51	
Multivariate analysis								
Abiraterone during/ after	0.32	0.035	0.53	0.044	N/E	N/E	0.33	0.020
Ra-223	0.11		0.28				0.31 -	
Yes vs No	0.91		0.98				0.84	

Table 3. Type and moment of treatment

Type of treatment prior, during and after	Before Ra-223	During/after Ra-223
Secundary hormonal therapy		
Total, n (%)	55 (50)	49 (45
Abiraterone	38	31
Enzalutamide	16	14

In a cost-effectiveness study a model was applied to estimate the amount in United States dollars (US$) paid for life-year gain (LYG) and QALY in the treatment of pre-chemotherapy and chemo-treated patients with castrate-resistant metastatic prostate cancer (mCRPC) [11]. Information about the drugs were obtained from their respective phase III clinical trial: abiraterone COU-AA-301 trial (1.000 mg oral during 1 year), enzalutamide AFFIRM (160mg oral during 1 year), Ra-223 ALSYMPCA (intravenous in 6 doses), including the gain in overall survival and the relative risk of death. The cost/LYG (life years gained) and cost/PoS (survival probability) were calculated both in US$ 230,000 for Ra-223, while the cost/LYG was 194,087 and 223,500 for abiraterone and enzalutamide, respectively.This costs were above the values proposed as a reference in the UK ($ 50,000/QALY (quality adjusted life-year) and in the United States ($50,000 for drugs that have a negative effect on patient's quality of life (QoL) and $ 100,000 for drugs with improvement reported in terms of QoL). The work suggested that docetaxel, the only drug without patent, offered the best value for the money spent on the largest return value regardless of the relative risk or calculation used. All other drugs evaluated, including sipuleucel-T, abiraterone, enzalutamide, and Ra-223 were considered to have excessive costs for their returns[11].

Other cost-effectiveness model was directed to evaluate the budget impact of enzalutamide for the treatment of metastatic CRPC in chemotherapy-naive patients, as compared to other drugs[12]. In their model,

adopting enzalutamide in the chemotherapy-naïve scenario had an annual incremental budget impact of $510,641, $4,426 per patient per year, $369 per patient per month, or $0.04 per member per month. Total treatment costs per patient in 12 months of enzalutamide was of U$102,204, of abiraterone was U$91.296 and of Ra-223 was U$81.780. Despite an increase in overall drug acquisition cost, the treatment of chemotherapy-naïve metastatic CRPC patients with enzalutamide was predicted to result in a savings of $4,186 in administration costs, $2,154 in monitoring costs, and $14,211 in adverse event costs over a 1-year time horizon compared to others options of therapy, including abiraterone and Ra-223[12].

Finally, a retrospective study with 25 patients who received Ra-223 as part of standard care reported the blood counts and PSA variations after therapy[13]. Patients receiving Ra-223 alone and concurrently with next-generation antiandrogens were compared. Fourteen patients received concurrent therapy during monthly Ra-223 with either enzalutamide (n = 8) or abiraterone (n = 6). For patients receiving either Ra-223 alone and with concurrent next-generation antiandrogen therapy, there did not appear to be any statistically significant differences between initial and nadir blood counts. Mean change from initial neutrophil count to nadir was 1.91/L in patients receiving Ra-223 alone, versus 2.31/L in patients receiving concurrent therapy with antiandrogens (p = 0.77). Mean change from initial hemoglobin value to nadir was 1.5 g/L in patients receiving Ra-223 alone, versus 1.8 g/L in patients receiving concurrent therapy with antiandrogens (p = 0.31). Mean change from initial platelet count to nadir was 52.31 cells/L in patients receiving Ra-223 alone versus 70.61 cells/L in patients receiving concurrent therapy with antiandrogens (p = 0.39). PSA was stable or decreased in 22% of patients receiving Ra-223 alone versus 35% of patients receiving combination treatment with antiandrogens (P = 0.24)[13].

DISCUSSION

Current overview of the treatment of mCRPC

Most prostate cancer patients treated with local or regional disease have positive outcomes, with a five-year survival rate near 100%. On the other hand, patients with metastatic prostate cancer at diagnosis have poor outcomes, with a median survival of approximately 3-4 years. The deprivation of androgens is the standard of care for the treatment of metastatic prostate cancer, since prostate cancer is the most sensitive of all cancers to endocrine therapy[14,15].

The deprivation can be done by surgical or pharmacological castration and aims testosterone reduction below 50ng/dL. The luteinizing hormone releasing hormone (LHRH) agonists are equivalent to orchiectomy and/or estrogen in achieving the aimed level of testosterone reduction, have reversible effects, and are currently the preferred first-line treatment for patients with metastatic prostate cancer[14]. Medical alternatives to this monotherapy are less supported by clinical trial data, and include LHRH antagonists and combinations of an agonist or orchiectomy with an androgen receptor inhibitor[16].

Evolution for castration-resistant prostate cancer affects nearly all patients with metastatic prostate cancer and is diagnosed by the following parameters: serum levels of testosterone lower than 50ng/dL, three consecutive increases in PSA levels, PSA progression despite intense hormonal manipulation, radiographic progression of bone lesions, or after at least 6 weeks of antiandrogens withdrawal[17].

The treatment of CRPC has improved over the past decade when new treatments were shown to be effective when added to androgen deprivation therapy, although maintenance of androgen deprivation therapy remains many times a necessary component of the treatment even during second and third-line therapies of CRPC. At this moment, there is no consensus about the correct order to be followed to treat such patients but, in the current state of the art, it is suggested to initially assess the patient's performance status and the spread of disease[17].

For individuals tolerant to treatment and mildly symptomatic or asymptomatic a wide range of drugs such as docetaxel, abiraterone, sipuleucel-T, or enzalutamide might be used For patients who do not tolerate well the first-line treatments and are asymptomatic, with no evidence of progression, it is suggested to offer regular monitoring and continued use of conventional anti-androgens (e.g., LHRH agonists). For men with symptomatic disease with or without visceral metastasis docetaxel may be indicated. The use of Ra-223 is approved for patients with CRPC who have symptomatic bone metastases, yet no malignant lymph nodes larger than 3 cm or visceral metastases. It can be used both before and after use of docetaxel with equivalent gains in overall survival. It was also observed that patients who completed the treatment with the radiopharmaceutical had greater benefits than those who changed for chemotherapy without completing the 6 treatment cycles, thus, it might be important to note the functional status of the patient before starting Ra-223 therapy[10]. The second-line treatments will depend on the drugs used in the first-line and may be: cabazitaxel, Ra-223, docetaxel, enzalutamide and abiraterone[17].

If there is evidence of advanced disease, it's

recommended to start treating with docetaxel chemotherapy, and in the case of progression to indicate the use of abiraterone or enzalutamide as a second line treatment. If the disease is slowly progressive, poor symptomatic or without visceral metastases, abiraterone or enzalutamide can be recommended as first line treatment. However, with the benefits seen in the COU-AA-301 and AFFIRM trials and their better tolerability, it's rational to consider abiraterone acetate or enzalutamide before chemotherapy in patients with contraindications to docetaxel or with poor general performance. Cross-resistance between abiraterone and enzalutamide, possibly related to the similarity in the mechanism of action, has been showed and there are also small, retrospective studies that, although with a potential bias due to the more advanced and aggressive disease, raise the possibility of decreased activity with docetaxel after either agent[18,19].

After the second-line treatment other options are possible and depend on the functional status of the patient and the previous stages of treatment. In a third-line treatment setting docetaxel can be used again or another antiandrogen agent, Ra-223 or cabazitaxel[17].

Ra-223 in combination with antiandrogens

There are still very limited data regarding the association of Ra-223 with anti-androgens in CRPC. In the retrospective study of Etchebehere et al.[10], it should be noticed that the number of patients taking abiraterone was more than twice that using enzalutamide. Such clinical preference may be based on the extrapolation of a possible synergistic interaction between abiraterone and radiotherapy, and the inference that the same may be true for the concomitant use of abiraterone and Ra-223, although other selection bias can not be ruled out[13]. Moreover, there is no information about whether the previous use of abiraterone with Ra-223 brought improvement in the evaluated parameters. Also, it is not possible to know whether the use of abiraterone was during or after treatment with Ra-223, which makes some other analysis of sequencing impossible.

Although there are no reports of increased incidence of bone marrow failure with the use of chemotherapy associated with Ra-223, the total number of cycles with Ra-223 was associated with a higher incidence of BMF which diverges from previous clinical trials and other analysis of toxicity in our reach. The study population is recognized by the authors as very heterogeneous and differs from previous studies. Although patients achieved a survival time of 12 months, shorter than the ALSYMPCA (median SG = 14 months), the patient population was different from that study. In the initial diagnosis before the first cycle of Ra-223, 82% of patients had skeletal tumor burden classified as high or intermediate, higher numbers than in ALSYMPCA study. Moreover, 12% had visceral metastases and 24% had lymph node metastasis and these patients were exclusion criteria of ALSYMPCA study. It arises, therefore, if in this population of patients with higher burden of disease or with visceral and lymph node metastases there are a higher risk of BMF in the treatment with Ra-223.

Besides the shown clear benefit of the associated use of Ra-223 with abiraterone, the reason why enzalutamide had not shown benefit in any of the parameters when associated with Ra-223 also deserves reflection and further analysis, maybe with more research. In the study the authors discuss that the comparative benefit of abiraterone against enzalutamide in this patient population could be due to a difference in patient selection, as in the case of patients who received abiraterone could have had a lower disease burden than those using enzalutamide. However, in that study, patients with metastatic CRPC initial ECOG status 2 and 3 were more prevalent in the abiraterone group than enzalutamide group, 14% *vs* 7%, respectively. Similarly, there were more patients undergoing chemotherapy before Ra-223 in the abiraterone group than in enzalutamide group (51 vs 46% respectively). Therefore, patients using Ra-223 and abiraterone had at least a similar load.

An ongoing study presented as a congress poster deserves mention, since it brings new data about this question[19]. The study is a phase IIIb trial, multicenter, prospective study that is checking the OS and the treatment safety of patients who have been treated with Ra-223. Among the 696 patients evaluated, 120 used abiraterone before treatment with Ra-223 and 25 used simultaneously, in addition, 59 patients used enzalutamide before therapy with Ra-223 and 15 concomitantly. The safety profiles in relation to therapy with Ra-223 were similar regardless of prior exposure or not to enzalutamide or abiraterone, similarly to the toxicity study included in this review[19]. Patients that had prior use of abiraterone or enzalutamide had also a higher rate of previous treatment with docetaxel and higher serum levels of alkaline phosphatase and PSA (theoretically they had a higher burden of disease and had been through more lines of treatment), but no significant variation in Ra-223 toxicity. Patients that used anti-androgens concomitant with Ra-223 were similar to those who did not use such drugs, except that PSA level and previous use of docetaxel were higher in the group with concomitant use of enzalutamide as compared to abiraterone or neither of the two drugs[19,20]. Contrarily to the study included in the review, in this prospective study patients that had used enzalutamide and Ra-223 were more

advanced in the disease and did not show improvement in overall survival[10,19,20]. Another fact to be noted is that among the patients who used abiraterone and Ra-223.32% had received prior enzalutamide. Among enzalutamide and Ra-223, 93% had received prior abiraterone, which may explain the lack of efficacy with enzalutamide due to cross-resistance. Regarding the OS: OS of patients who received Ra-223 after treatment with abiraterone or enzalutamide appears to be similar to the rest of the population of the study and patients receiving therapy with Ra-223 concurrently with enzalutamide or abiraterone (as first-line therapies) a higher OS compared to the overall study population. It raises indications that prior therapy with antiandrogens does not alter the effectiveness of Ra-223.

The possibility of combination of Ra-223 with the new antiandrogens agents such as abiraterone and enzalutamide raises questions about their safety together. The literature indicates that the isolated treatment with each of these drugs has excellent tolerability profile. All included studies in this review and the mentioned poster, confirm that the Ra-223 combination with abiraterone and Ra-223 with enzalutamide has similar toxicity levels to those seen in patients who have exclusive use of therapy with Ra-223[10,13,19,20]. This seems to occur because the toxicity of antiandrogens does not overlap the toxicity of Ra-223 and allows a secure association and a new range of possibilities of treatment.

Regarding cost-effectiveness, the cost per LYG is high for all drugs previously mentioned[11]. This raises questions about the cost-effectiveness of these drugs in a public health system such as the Brazilian Unified Health System (SUS), although an adequate evaluation should be performed in this specific contexts. The other study assessing the budget impact of an imaginary population of 1 million of habitants argued that the total spent on treatment with Ra-223 is significantly lesser than with abiraterone or enzalutamide, but enzalutamide compensated financially for generating further less side expenses[12].

Another poster that was not included in this review deserves mention, this one assessing cost-effectiveness using the Markov's model in patients previously treated with docetaxel, comparing Ra-223 with other drugs, including abiraterone and enzalutamide[21]. Effectiveness, symptomatic skeletal events (SSE's), safety and QUALY's were obtained from Phase III trials of such drugs through meta-analysis. SSE's costs were taken from Dutch sources. The lifetime lower costs of Ra-223 in comparison with enzalutamide are driven by lower costs of drugs and, same as abiraterone, of SSE's treatment costs[21].

From all this information we might conclude that the cost of these drugs is significant in a scenario where the survival gains are modest due to the severity of the disease. The drugs do not seem to have great differences in relation to total spending and there is still no consensus on the most cost-effective treatment in the short and long term. Moreover, it is complex to transpose results from these studies in developed countries to Brazil, where the economic impact of these treatments on the health system may be greater. However, there is always a fair debate whether it is ethical to put a financial limit to effective treatments for serious illnesses like CRPC.

Considering the studies that directly evaluated the use of Ra-223 with abiraterone acetate or enzalutamide we must make some points. In one, 110 patients were evaluated while in the other only 25[10,13]. Furthermore, there was wide variation in the demographic spectrum of patients, the specters of disease and therapies previously and in current use. Moreover, both works consist of case series, with a low degree of evidence in the principles of evidence-based medicine. Thus, for more detailed analysis and more accurate conclusions about the association and sequential use of Ra-223 with abiraterone acetate or enzalutamide, more robust studies in terms of sample size and degree of evidence are necessary[22].

Future perspectives

The main limitation of the present study was the scarcity of original articles about the association or concomitant use of Ra-223 with enzalutamide or abiraterone. This fact may be due to the actuality of the development and evaluation of these drugs (e.g. ALSYMPCA phase III trial were released in 2013), and to the delay in time from the entry of articles in the databases to complete indexation with medical subject heading (MeSH) terms. There are ongoing clinical trials that aim to precisely study the association or concomitant use of these drugs, therefore in the next few years this situation tends to change. We present below (Table 4) the current trials that englobe directly this topic or may provide new data to study the association or concomitant use of these drugs.

CONCLUSION

Further studies are necessary to evaluate the best efficacy of concurrent or sequential treatment of Ra-223 with the new antiandrogens, however, preliminary studies indicate that there may be a positive synergistic effect of abiraterone associated with Ra-223, a fact that, up to date, was not observed in Ra-223 association with enzalutamide. In addition, new evidence shows that concomitant or sequential treatment with these drugs does not impact on toxicity. The costs of these drugs are considerable and greater understanding of the effectiveness of the drugs and on the time of use or sequencing can lead to a more rational and cost-effective use[10,13,19,20].

Table 4. Current clinical trials

	NCT02043678	NCT02034552	NCT02225704	NCT02729103	NCT02199197	NCT02097303	NCT02507570
Official Title	A Phase III Randomized, Double-blind, Placebo-controlled Trial of Radium-223 Dichloride in Combination With Abiraterone Acetate and Prednisone/Prednisolone in the Treatment of Asymptomatic or Mildly Symptomatic Chemotherapy-naïve Subjects With Bone Predominant Metastatic Castration-resistant Prostate Cancer (CRPC)	A Randomized Open-label Phase IIa Study Evaluating Quantified Bone Scan Response Following Treatment With Radium-223 Dichloride Alone or in Combination With Abiraterone Acetate or Enzalutamide in Subjects With Castration-resistant Prostate Cancer Who Have Bone Metastases	A Phase II Study of Radium-223 in Combination With Enzalutamide in Progressive Metastatic Castrate-Resistant Prostate Cancer	Treatment Patterns, Mortality, Healthcare Resource Utilization, and Costs in Patients With Prostate Cancer With Bone Metastases: A Retrospective Database Analysis	A Phase 2 Randomized Study Comparing Radium Ra 223 Dichloride Plus Enzalutamide With Enzalutamide Alone in Men With Metastatic Castration Refractory Prostate Cancer	Open Label Phase Two Trial of Radium Ra 223 Dichloride With Concurrent Administration of Abiraterone Acetate Plus Prednisone in Symptomatic Castration-Resistant (Hormone-Refractory) Prostate Cancer Subjects With Bone Metastasis	Open Label Phase Two Study of Enzalutamide With Concurrent Administration of Radium Ra 223 Dichloride in Castration-Resistant (Hormone-Refractory) Prostate Cancer Subjects With Symptomatic Bone Metastasis
Estimated Completion Date	December 2020	June 2018	Not provided	June 2016	June 2019	December 2015	Not provided
Estimated Primary Completion Date	December 2017 (final data collection date for primary outcome measure)	July 2016 (final data collection date for primary outcome measure)	December 2017 (final data collection date for primary outcome measure)	June 2016 (final data collection date for primary outcome measure)	June 2019 (final data collection date for primary outcome measure)	December 2015 (final data collection date for primary outcome measure)	February 2017 (final data collection date for primary outcome measure)
Recruitment Status	Recruiting	Active, not recruiting	Recruiting	Not yet recruiting	Recruiting	Study completed (results not provided)	Recruiting
Estimated Enrollment	800	62	44	1000	50	40	40

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