Review

Bone health and therapeutic agents in advanced prostate cancer

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Abstract

Prostate cancer is the most frequent genitourinary tumor worldwide. Maintaining an optimum bone health throughout the natural course of prostate cancer is an important aspect in the management of this disease, particularly in this at risk population of older and frail patients who experience bone loss related to androgen-deprivation therapy (ADT) and/or patients who develop bone metastases. The number of treatment options for advanced prostate cancer that combine ADT with docetaxel, new hormonal agents and/or radiotherapy has increased substantially in recent years. Bisphosphonates and other bone targeted agents such as denosumab have shown an improvement in bone mineral density and are suited for patients with treatment-related osteoporosis and/or bone metastases with an increased risk of skeletal-related events (SREs). In this context, the aim of this review is to analyse key aspects of bone health and therapies that can prevent the occurrence of SREs throughout the clinical course of prostate cancer, and how to combine them with new available treatments in this setting.

Keywords: Bone health; Prostate cancer; Skeletal-related events; Osteoporosis; Denosumab; Bisphosphonates

1. Introduction

Prostate cancer (PCa) is the most frequent solid tumor in males and androgen-deprivation therapy (ADT) plays an important role in its treatment, both as part of definitive therapy and in advanced or metastatic stages, where it continues to be a first line treatment. It is estimated that 50% of patients with PCa will receive ADT at some point during the natural history of their disease [1].

It is widely known that the use of ADT is associated with osteopenia, which can evolve into osteoporosis, and an increased risk of fracture. This deficit in mineralization is related to a reduction in testosterone levels and a reduced aromatization of estrogens, which are important factors in bone health [2]. Osteopenia occurs in up to 85% of cases and osteoporosis ranges, according to different studies, between 9–53% [2,3]. The magnitude of this osteopenia is associated with the duration of androgen suppression (among other factors), although several studies show that the most important loss in bone mineral density (BMD)—up to 10% depending on the location— occurs during the first year of ADT [1,3,4]. After this year, the rate of BMD loss slows down to approximately 2% per year, which still represents between twice and four times the physiological loss in the general male population. Consequently, the risk of fracture over the following 5 years increases from 12.6% in untreated patients to 19.4% in those who receive ADT, with the subsequent impact in quality of life and survival [5,6].

For all the above reasons, it is important to conduct a proper evaluation to establish preventive measures. However, according to the results of a Canadian study evaluating ADT management, only 58.8% of patients had a basal densitometry and only 20.3% were re-evaluated during follow-up, which led to undertreatment (only 13% were treated with bisphosphonates) [3].

PCa tends to metastasize in the bones. Tumor cells usually secrete promoting factors of bone formation, such as bone morphogenic proteins (BMPs) and RANK-L inhibitors, which attenuate osteoclastic activity. This is the reason why most bone metastases are osteoblastic, although mixed, osteolytic or even metastases with no radiological evidence are reported in the literature.

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These lesions frequently generate pain and skeletal-related events (SREs) that can be caused by secondary osteopenia due to prolonged ADT use or by pathologic fractures secondary to a bone metastasis. The accumulated incidence of these SREs in the following two years after the diagnosis of metastatic PCa is 41.9% [7].

Bisphosphonates and drugs that target osteoclast receptors such as denosumab, in addition to calcium and vitamin D supplements, play an important role in the prevention and reduction of osteopenia/osteoporosis in patients with bone metastases and in those receiving ADT [8,9]. The treatment options for advanced PCa that act on bone metastasis by combining ADT with docetaxel, new hormonal agents and/or radiotherapy have substantially increased in the last few years and highlight the necessity of an adapted bone protection strategy [10].

The aim of this review is to analyse the correct assessment of bone health, as well as the main targeted treatments and their association with specific oncological treatments for PCa patients.

2. Bone health assessment and prevention

2.1 Bone health assesment in the management of patients with PCa

Bone tissue is subjected to a continuous process of remodeling based on the coordinated generation and resorption mediated by osteoblasts and osteoclasts, respectively. Osteoclast activity is regulated, among other factors, by the receptor activator of nuclear factor κB (RANK) and osteoprotegerin (OPG). The union of RANK with its ligand (RANKL) favors the survival of osteoclasts, whereas the union of RANK with OPG inhibits their activity. Therefore, BMD depends on a cellular and molecular balance.

Osteoporosis is a metabolic bone dysfunction defined by the loss of bone tissue and the deterioration of its microarchitecture. The physiology of bone remodeling is mediated by multiple cytokines and hormones. Estrogens inhibit bone resorption, whereas androgens promote bone formation. An alteration in this balance explains why this group of patients have a loss of BMD and the onset or worsening of osteoporosis [11].

Osteoporosis induced by ADT can be severe: it causes an important deficit in BMD during the first 6–12 months of treatment, 17.3% higher than males untreated for PCa, and it is associated with a higher risk of fracture [12]. The prevalence of osteoporosis in this group of patients varies between 10–40% and increases with age and ADT duration [13,14]. This reinforces the importance of conducting an adequate evaluation to prevent BMD deficit in all patients that are going to start treatment with ADT [14].

The use of ADT in addition to other systemic treatments in more advanced stages of PCa, such as next generation anti-androgens, glucocorticoids or radium-233 (Ra-233) results in increased bone resorption and, consequently, decreased BMD [15,16], which translates into a higher risk

of suffering SREs [17]. Moreover, bone metastasis related to PCa poses a higher risk of pathologic fractures. It is important to identify those patients at risk given that it has already been reported in multiple clinical trials that the combination of bone-targeted therapies and different treatments for advanced PCa have a positive impact both in pain control and reduction of SREs [18–20].

Before any treatment for PCa is started, the assessment of BMD is useful for identifying those patients with osteopenia or osteoporosis and for establishing the risk of fracture. There is a direct and progressive association between the loss of BMD and fractures, as the risk doubles for each decrease in standard deviation [21]. The basic tool for evaluating BMD is bone densitometry through a dual energy X-ray absorptiometry of the femoral neck.

The World Health Organization establishes a cut-off point to define osteoporosis (and therefore a high risk of fracture) of 2.5 standard deviations below the average of a female young adult (T-score ≤2.5), and the same is used for males [22]. Although BMD assessment has high specificity for risk of fracture, its sensitivity is low [23]. For this reason, it is recommended to complement the information provided by bone densitometry with clinical risk factors. There is a well-established association between the risk of bone fracture and other SRES, with the following risk factors: age >65, body mass index (BMI) <24, tobacco, alcohol, previous history of falls and fractures, and family history of hip fracture [24].

To help with the evaluation and decision-making in this clinical scenario, various tools have been developed as algorithms that calculate the risk of fracture from a series of risk factors exclusively or with the addition of BMD. For instance, the Fracture Risk Assessment Tool (FRAX) is an algorithm that provides an estimation of the 10-year risk of osteoporotic fracture for each person, with the advantage of being validated for independent cohorts in several countries [25].

Despite the obvious importance of assessing bone health in patients with PCa, there are no clearly established cut-off points to guide the start of bone-targeted therapies or standard intervals to conduct tests during follow-up.

Briot *et al*. [26] published a series of recommendations to evaluate which patients with PCa under ADT have a risk of fracture and, therefore, would be candidates for treatment with bone-protecting agents (BPA). They propose the evaluation of BMD before the start of ADT and recommend the prescription of antiresorptive therapy if T score <–2.5 or between –1.5 and 2.5 with concurrent factors such as BMI <19, age >75 years, cardiovascular disease, or frequent falls [26]. Furthermore, European guidelines on the treatment of genitourinary tumors recommend treatment with antiresorptive therapy if the annual bone loss is >5% in patients receiving ADT [27].
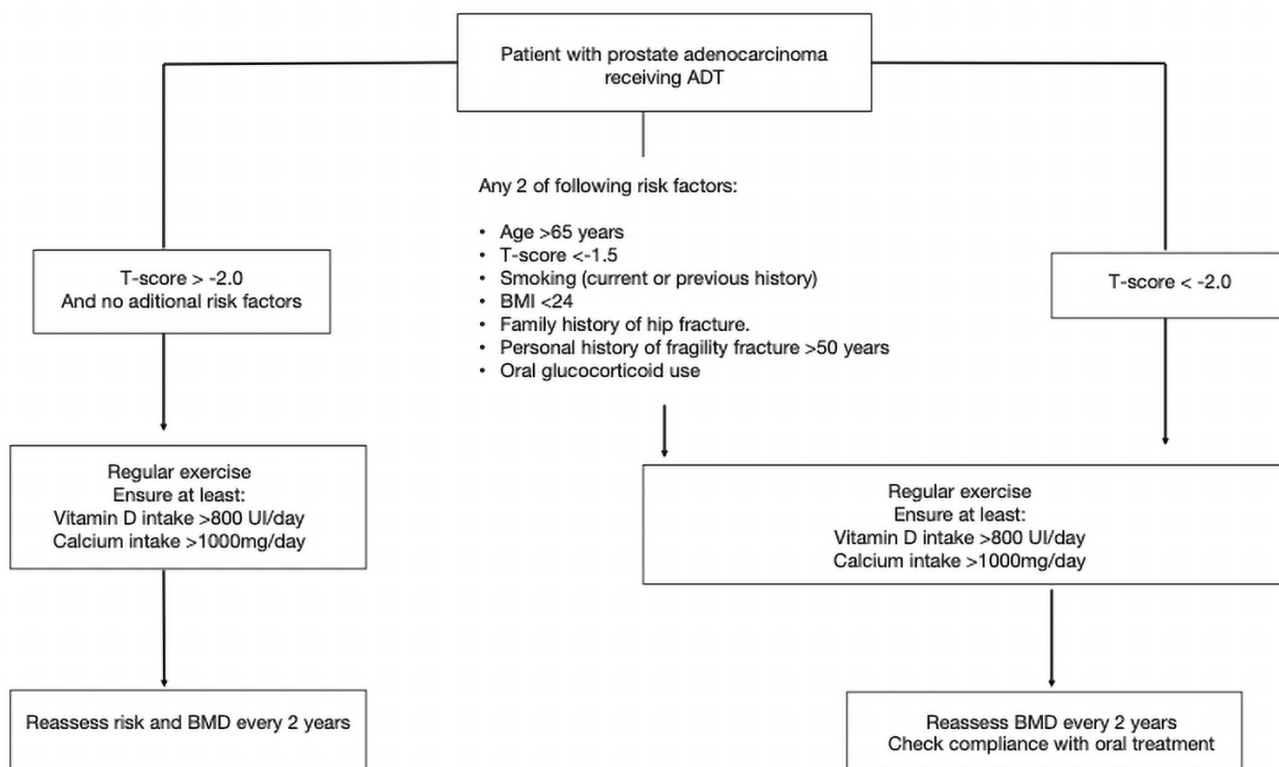
Fig. 1. Algorithm for the management of bone health in patients with advanced prostate cancer receiving treatment with androgenic suppression. ADT, androgen deprivation therapy; BMI, body mass index; BMD, bone mineral density. Adapted from Hadji *et al*., 2017 [29].

A reasonable approximation to assess bone health in PCa patients and the start of BPA is the proposal of the European Association of Medical Oncology (ESMO), an adaptation of the recommendations by Hadji *et al*. [28,29] or women under aromatase inhibitors (Fig. 1, Ref. [29]).

Because the FRAX score is not well optimized for PCa patients on ADT, some centres proactively start Vitamin D and bisphosphonates in all patients receiving long term ADT. Studies show that 77% of men on ADT exceed the FRAX threshold for prophylactic therapy hence population based therapy is likely to be of benefit [30].

2.2 Prevention and therapeutic strategies

2.2.1 Physical exercise

Experts recommend physical activity in patients with cancer due to its numerous health benefits. While there is no solid evidence that it specifically prevents the loss of BMD and the risk of fracture in patients receiving ADT [31], it is an effective strategy for generating significant benefits in general heath.

Furthermore, exercise also has a positive impact on other ADT-induced side effects such as obesity and sarcopenia, which are also known risk factors for bone health.

The European Association of Urology (EAU), ESMO and the National Comprehensive Cancer Network (NCCN) guidelines also prescribe following other lifestyle changes;

smoke cessation, limitation of alcohol intake and healthy weight due to their known impact on bone health [27,28, 32].

2.2.2 Calcium and vitamin d supplements

The adequate intake or supplementation of calcium and vitamin D in patients receiving ADT supplements is reflected in clinical guidelines [28,33]. Studies that employ densitometry for patient evaluation have reported that these supplements attenuate the loss of BMD during ADT , especially during the first year [34]. However, there is no trial to date that has compared the intake of supplements vs. placebo in patients with non-metastatic PCa receiving ADT.

The EAU, NCCN and ESMO recommend the supplementation of vitamin D deficit in patients under ADT: 800–1000 UI/day of vitamin D3 and 1000–1200 mg/day of calcium (from food and supplements). This prescription should be continued if introducing BPA [35]. Currently, there are no guidelines on the frecuency of vitamin D level testing.

2.2.3 Bone-protecting agents

Bisphosphonates are pyrophosphate analogues. They inhibit the effect of prostacyclins and cytokines in the bone tissue and reduce the number of osteoclasts through the

downregulation of the reticuloendothelial system, thus preventing bone resorption by inducing the apoptosis of osteoclasts. Bisphosphonates include zoledronic acid (ZA), risedronate, pamidronate, ibandronate, alendronate, etidronate and clodronate, with ZA being the most employed intravenously (iv) in PCa patients.

Denosumab is a human monoclonal antibody (IgG2) that binds to RANKL with great affinity and specificity. RANKL is expressed as a soluble or transmembrane protein and is essential in the formation, function and survival of osteoclasts, the only cell responsible for bone resorption. The increase in osteoclastic activity stimulated by RANKL is a key mediator of bone destruction in metastatic disease. The union of denosumab to RANKL prevents RANKL-RANK interaction, thus blocking the transduction signal that stimulates the formation, activation, and survival of osteoclasts. This agent is administered subcutaneously.

Both bisphosphonates and Denosumab are well tolerated. Except for the acute reaction that can be caused by the iv administration of ZA, side effects are rare if following the recommended dose and treatment schedule. Special precautions should be taken regarding the renal toxicity of ZA: a dose reduction is advised with a baseline creatinine clearance of 30 to 60 mL/min and should not be administered if >30 mL/min [28] . Electrolyte imbalance is associated with both treatments, with hypocalcemia being more common with denosumab [10]. Denosumab can produce mandibular osteonecrosis, whereas no differences in the incidence of this side effect are observed when comparing ZA to placebo [36], therefore, a dental evaluation is recommended before the start of antiresorptive agents.

In terms of toxicity in patients receiving treatment with these drugs while receiving ADT and with no bone metastases, no cases of mandibular osteonecrosis have been reported in clinical trials [9,37,38].

3. Prevention of osteoporosis and bone metastases in non-metastatic locally advanced prostate cancer

3.1 Non-metastatic hormone-sensitive prostate cancer

In this scenario, various trials have evaluated the role of ZA and have found a benefit in the protection from osteoporotic events induced by ADT and the increase in BMD. However, no differences have been reported in terms of prevention of fractures or quality of life. For this reason, ZA is not approved for this specific setting and its use depends on the clinical judgement of the prescribing physician. The doses in these studies were 4 mg every 3 or 12 months [37–40]. However, a dose of 5 mg annually is recommended as a professional consensus [26]. Oral BPA may be considered as an alternative.

Denosumab is the only drug approved by the Food and Drug Administration and the European Medicines Agency for the prevention of pathologic fractures caused by osteoporosis in patients under ADT. In the pivotal trial that

led to this approval, after a follow-up of 36 months, patients treated with denosumab presented less vertebral fractures and an increase in BMD in comparison to the placebo group, with statistically significant differences in both cases [9]. The recommended dose in this setting is 60 mg subcutaneously every six months.

3.2 Non-metastatic castration-resistant prostate cancer

Treatment for patients with non-metastatic castration-resistant prostate cancer (nmCRPC) has drastically changed with the introduction of next generation inhibitors of the androgen receptor. These drugs were approved after showing a significant increase in metastasis-free survival (MFS) compared to placebo in three randomized phase III clinical trials [41–43]. The results of these three studies suggest that, in patients with nmCRPC these new agents are highly effective at postponing development of metastases. In all three trials the percentage of patients with added treatment with bone-targeted therapies was low: 11% (enzalutamide) vs. 10% (placebo) in PROSPER, 10.2% vs. 9.7% in SPARTAN and 3% vs. 6% in ARAMIS. Therefore, no conclusions can be drawn on the concomitant treatment with both therapies.

The benefit of denosumab has been investigated in a phase III clinical trial that included 1432 patients with CRPC. Of these, 716 were nmCPRC and were treated with a monthly dose of 120 mg of subcutaneous denosumab. A significant increase in MFS was observed when compared to placebo (29.5 vs. 25.2 months; hazard ratio (HR): 0.85; $p = 0.028$). However, this was at the expense of mandibular osteonecrosis in 5% of participants, which explains why denosumab is not currently approved for the prevention of metastasis in this subset of patients [44].

Regarding bisphosphonates, although preclinical data suggest their antitumor activity, they have not shown a decrease in the appearance of bone metastases in this subgroup of patients [45].

4. Prevention of skeletal-related events in metastatic prostate cancer

4.1 Metastatic castration-resistant prostate cancer

ZA is the only bisphosphonate that has demonstrated a reduction in SREs related to bone metastases in men with metastatic castration-resistant prostate cancer (mCRPC) [28]. Saad *et al*. published the results of a multicenter randomized trial that compared ZA vs. placebo in this group of patients. The evaluated dose was 4 mg every three weeks and 8 mg every three weeks (which was later reduced to 4 mg) against placebo. Patients in the placebo group had more SREs than those treated with 4 mg ($p < 0.021$) or 8 mg/4 mg of ZA. Pain and need of analgesia were higher in the placebo group, but no differences were found in disease progression, performance status or quality or life. This study defined the tolerance profile of ZA, with 4 mg being the optimal dose compared with 8 mg [46]. After 24

months of treatment, the annual incidence of SREs was significantly higher in the placebo group ($p < 0.005$). Median time to the first SRE was reached in both groups, being six months longer for ZA ($p < 0.009$) [47]. In further analyses, it was observed that ZA reduced the percentage of patients with ≥ 1 SREs and delayed the onset of bone pain in patients who were asymptomatic at the start of the study [48–50]. ZA also showed a non-statistically significant tendency towards a prolonged overall survival (OS) in patients with mCRPC [51].

Pan *et al.* [52] evaluated the efficacy and safety of the combination of ZA and docetaxel in CRPC with bone metastases in a prospective study of 105 patients. The combined treatment presented better OS ($p = 0.02$) and bone MFS ($p < 0.05$) than docetaxel and placebo, with no differences in toxicity [52]. Furthermore, TRAPEZE trial suggested that ZA could have a role as maintenance therapy after docetaxel due to an improved interval free of SRE, mainly after disease progression [53].

Between these two treatments, denosumab has demonstrated to be superior to ZA in patients with bone metastases [54]. Fizazi *et al.* [10] published the results of a double-blinded, randomized study in patients with mCRPC. 120 mg of subcutaneous denosumab every four weeks were superior to 4 mg of iv ZA. Denosumab significantly reduced the risk of appearance of a first SRE and posterior skeletal events compared to ZA ($p < 0.008$), although no differences in OS were observed. In a subanalysis, denosumab showed a benefit in the delay of pain progression compared to ZA by increasing the time to the onset of moderate-severe pain ($p < 0.0001$) (Table 1) [55].

It is recommended to start ZA or denosumab in patients with CRPC and bone metastases, even if they are asymptomatic, in doses of 4 mg of iv ZA every four weeks and 120 mg of subcutaneous denosumab every month [56].

Regarding other treatments available in mCRPC, Ra-223 is an alpha emitter radionucleotide tailored for the treatment of patients with osteoblastic metastases, with benefits in OS and SREs, and manageable side effects. Various trials have studied its combination with BPA and/or next generation anti-androgens [57].

The ERA 223 trial combined abiraterone plus prednisone with Ra-223 or placebo in patients with mCRPC who had not received previous chemotherapy [17]. The study showed, contrary to expectations, that the addition of Ra-223 did not improve SRE-free survival and was, in fact, associated with a higher risk of fracture, mainly in bone sites with no metastases. However, post-hoc analysis showed that the increase in bone fractures was particularly observed in patients not receiving BPA. These findings reinforce the importance of adequate monitoring bone health and the use of BPA [58]. These results are not replicated with the combination of enzalutamide and Ra-223 as the results of ERA 223 trial has led to the mandatory use of BPS in the phase III EORTC-1333/PEACE III trial, which treats patients with Ra-223 plus enzalutamide vs. enzalutamide alone. An interim safety analysis was performed and confirmed that, in absence of BPA, fracture risk was increased and, more importantly, the risk remains almost nonexistent with a preventive continuous administration of BPA. Again, this highlights the value of BPA in this patient population [57].

There are data that support the concomitant administration of Ra-223 with osteoclast-targeted agents. The phase III study ALSYMPCA recruited 921 patients with mCRPC with symptomatic bone metastasis and no visceral lesions and randomized them to receive 50 KBq/Kg of Ra-223 every four weeks or placebo [59]. OS, the primary endpoint of this study, was reported as 14.9 months in the experimental arm vs. 11.3 in the placebo arm (HR: 0.70; $p < 0.001$). 41% of patients received bisphosphonates and a delay in the onset of SREs was observed in this subgroup (19.6 vs. 10.2 months; HR: 0.49; $p = 0.00048$). At present, international guidelines recommend that, in men with mCRPC previously treated with docetaxel (or unsuitable for docetaxel) and one anti-androgen and who present bone pain, Ra-223 should be considered as a treatment option to prolong life, reduce symptomatic SREs and improve quality of life. Concomitant use with abiraterone and prednisone is advised against due to an increased risk of fracture [60].

As for the new anti-androgens, a post hoc analysis of the COU-AA-302 trial reported that, in patients with no previous chemotherapy, bone-directed therapies administered concomitantly with abiraterone and prednisone were associated with improved clinical results compared to previous studies in terms of OS, time to worsening in performance status and pain control [18]. Likewise, the PREVAIL study reported a 29% reduction in the risk of death and prolonged time to the first SRE in patients with no previous chemotherapy who received enzalutamide [61].

4.2 Metastatic hormone-sensitive prostate cancer

ZA has been evaluated in patients with metastatic hormone-sensitive prostate cancer (mHSPC). In the STAMPEDE trial, the addition of ZA to standard of care (SOC) treatment was not associated with an improvement in OS, disease free survival or delay in SRE [19]. Similar results were obtained in the CALGB 90202 study, which evaluated ADT plus ZA versus ADT plus placebo, and found no differences in the time to the first SRE, OS or grade ≥ 3 toxicity [62]. The ZAPCA trial also reported comparable results [63] (Table 1). There are still no published data on the role of denosumab in this setting.

For the reasons above, the use of ZA or denosumab is not approved for clinical practice in mHSPC for purposes of disease control.

In contrast, several clinical trials have shown benefits in OS and radiographic progression-free survival (rPFS) associated with next generation hormonal therapies [64–67]. The ARCHES trial [68] and the ENZAMET trial laid the

Table 1. Randomized studies with zolendronic acid and denosumab in mCRPC y mHSPC.

Study/author name	Study population	Treatment arms	Primary endpoints	Results
Saad	mCRPC	ZA 4 mg/3 weeks vs. placebo	SRE	ZA reduced SRE compared to placebo, $p = 0.021$
Fizazi	mCRPC	Denosumab 120 mg/4 weeks vs. ZA 4 mg/3 weeks	Time to first SRE	Median time to first SRE and further SREs was superior with denosumab ($p < 0.008$)
TRAPEZE	mCRPC	Docetaxel + prednisolone vs. Docetaxe + prednisolone + ZA vs. Docetaxe l + prednisolone + strontium-89 vs. Docetaxel + prednisolone + ZA + strontium-89	CPFS (pain progression, SRE or death)	ZA did not improve CPFS, but delayed the time to first SRE
STAMPEDE	mHSPC	SOC vs. ZA + SOC vs. SOC + docetaxel vs. SOC + ZA + docetaxel	Overall survival	ZA did not improve overall survival or delayed the appearance of metastasis
CALGB 90902	mHSPC	ZA 4 mg/4 weeks vs. placebo	Time to first SRE	No differences in time to SRE or survival
ZAPCA	mHSPC	ZA + ADT vs. ADT	Time to treatment failure and time to first SRE	Time to first SRE longer in ZA + ADT ($p < 0.009$) In PSA <200, ZA + ADT delayed time to treatment failure ($p < 0.023$)

mCRPC, metastatic castration-resistant prostate cancer; ZA, zolendronic acid; SER, skeletal-related events; CPFS, clinical progression-free survival; mHSPC, metastatic hormone-sensitive prostate cancer; SOC, standard of care; ADT, androgen-deprivation therapy.

Table 2. Selected clinical trials of bone modifying agents alone or in combination with second generation hormonal treatments in prostate cancer.

NCT number	Study type	Name	Primary endpoint	Secondary endpoints	Estimated enrollment	Stage
NCT03732820	Phase 3	A Randomised, Double-blind, Placebo-controlled, Multicentre Phase III Study of Olaparib Plus Abiraterone Relative to Placebo Plus Abiraterone as First-line Therapy in Men With Metastatic Castration-resistant Prostate Cancer (PROpel Study).	● Radiological progression-free survival (rPFS)	● Overall survival (OS) ● Time to first subsequent anti-cancer therapy or death (TFST) ● **Time to a Symptomatic Skeletal-Related Event (SSRE)** ● Time to pain progression (TTPP) ● (...)	904	Recruiting
NCT04050397	-	Exercise Intervention to Reduce Adverse Quality of Life Effects From Androgen Deprivation Therapy for Prostate Cancer - Randomized Clinical Trial.	● Overall quality of life ● Prostate cancer-specific quality of life	● **Bone fractures** ● **Time to prostate cancer death** ● (...)	40	Recruiting

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Table 2. Continued.

NCT number	Study type	Name	Primary endpoint	Secondary endpoints	Estimated enrollment	Stage
NCT04507698	Phase 3	INTense Exercise foR surVivAL Among Men With Metastatic Castrate-Resistant Prostate Cancer (INTERVAL - MCRPC): A Multicentre, Randomised, Controlled, Phase III Study.	● Overall Survival	● Disease progression ● **Symptomatic Skeletal Related Events** ● Analgesic/Opiate Use ● (…)	80	Recruiting
NCT04549207	Phase 4	A Randomised Trial Comparing Continuation or De-escalation of Bone Modifying Agents (BMA) in Patients Treated for Over 2 Years for Bone Metastases From Either Breast or Castration-resistant Prostate Cancer (REaCT-Hold BMA).	● Health related quality of life scores	● **Symptomatic Skeletal Event (SSE)** ● **Time to development of Symptomatic Skeletal Event** ● **Symptomatic Skeletal Event-free survival** ● Skeletal morbidity ● (…)	240	Recruiting
NCT02051218	Phase 3	Prevention of Symptomatic Skeletal Events With Denosumab Administered Every 4 Weeks Versus Every 12 Weeks - A Non-Inferiority Phase III Trial.	● Time to first on-trial symptomatic skeletal event	● Toxicity (focus on hypocalcemia and osteonecrosis of the jaw) ● **Time to first and subsequent on-trial SSE** ● Quality of Life ● (…)	1181 (actual enrollment)	Active, not recruiting
NCT03869762	Phase 2	A Phase II Study of Denosumab in Combination With Enzalutamide in Progressive Metastatic Castrate-resistant Prostate Cancer and Bone Metastases.	● Radiographic progression-free survival (rPFS)	● Overall survival ● PSA progression free survival ● **Time to first skeletal-related event** ● Pain assessment	6 (actual enrollment)	Suspended (Insufficient accrual)
NCT02194842	Phase 3	A Randomized Multicenter Phase III Trial Comparing Enzalutamide vs. a Combination of Ra223 and Enzalutamide in Asymptomatic or Mildly Symptomatic Castration Resistant Prostate Cancer Patients Metastatic to Bone.	● Radiological progression-free survival	● Overall survival ● prostate cancer specific survival ● **First symptomatic skeletal event** ● Time and incidence of first skeletal progression-free ● (…)	560	Recruiting
NCT02730338	Phase 3	INTense Exercise foR surVivAL Among Men With Metastatic Prostate Cancer (INTERVAL – GAPA4): a multicentre, randomised, controlled phase III.	● Overall Survival	● Disease progression ● **Symptomatic Skeletal Related Events** ● Analgesic/Opiate Use ● (…)	866	Recruiting

groundwork for the use of enzalutamide in patients with mHSPC. This last study reported an increase in 3-year OS (80% vs. 72%; HR: 0.39; $p < 0.001$) and rPFS ($p = 0.005$) in favor of enzalutamide. In fact, in the ENZAMET study, the use of bone-directed therapies was used as a stratification factor (9.8% of patients). In the subgroup analysis, no clear clinical benefit was observed for OS (HR: 1.77; 95% confidence interval (CI) 0.83–3.77; $p = 0.006$) [66]. Similarly, the TITAN trial reported a benefit in the apalutamide group compared to placebo, both in OS (82.4% vs. 73.5%; HR: 0.67; 95% CI 0.51–0.89; $p = 0.005$) and rPFS (68.2% vs. 47.5%; HR: 0.48; 95% CI 0.39–0.60; $p < 0.001$), although no significant differences in time to first SRE were observed [67]. At present, there are no randomized prospective studies on the sequence of hormonal therapies than can allow us to define the optimal timing for these types of treatments or their combination with bone-directed therapies. Additional studies are needed to solve an issue that is appearing more and more frequently in the management of these patients.

5. Dose, scheme and treatment duration of bone-protecting agents for the prevention of skeletal-related events

Regarding the optimal administration of BPA, several trials compare dose escalation of both denosumab and ZA [69]. The results of a multicenter study that included patients with bone metastases from breast cancer and CRPC have recently been published. Of the 263 participants, 39.2% had mCRPC. The administration of 4 mg of iv ZA or 120 mg of subcutaneous denosumab every 12 weeks was not inferior to the monthly scheme in terms of quality of life. These results are consistent with previously published data. While we wait for the results of the REDUSE trial [70], de-escalating the dose of denosumab and ZA seems like a reasonable clinical decision based on the available evidence [71]. It must be noted that the most recent ESMO recommendations, while they also suggest de-escalation of ZA, still recommend the monthly denosumab. However, this last update was issued prior to the publication of this trial [28].

The optimal treatment duration of BPA for the prevention of SRES in patients with metastatic PCa is not well established. In the 2019 Advanced Prostate Cancer Consensus Conference, 61% of panelists agreed on maintaining therapy for 24 months in patients with mCRPC, 4% suggested treatment for five years and 31% opted for indefinite treatment [14]. The American Society of Clinical Oncology (ASCO) conducted a review of recommendations for bone health in patients with PCa. Relative to treatment duration with ZA or denosumab, they established that, although pivotal studies set a maximum of 24 months, the optimal duration to prevent SREs in mCRPC is not well define [60] and further trials with longer follow-up are needed to gather more information on this topic.

6. Novel therapies

Recent studies focus on the identification of new therapies that may break the vicious cycle of bone metastasis by targeting osteoclasts. These include: endoteline antagonists (e.g., zibotentan), c-Scr inhibitors (e.g., dasatanib) and tirosin-kinase inhibitors (e.g., cabozantinib) [72–74]. However, despite their activity in other tumors, they haven't managed to show significant results for PCa in phase III randomized trials.

7. Future directions

The survival improvement in patients with PCa is linked to the increase in the number of available treatments and the magnitude of the benefit of these therapies, which can have a cumulative impact in bone health over the years. Nowadays, most ongoing studies on the usefulness of new drugs in PCa include rPFS or time to first SRE as secondary endpoints (NCT03732820) (Table 2).

The assessment of bone health and the optimization of treatments to avoid its deterioration is key to elude the morbidity and mortality associated with the cancer-related loss of BMD. Non-pharmacological interventions such as lifestyle changes and physical activity are important to prevent SREs associated with ADT. For this reason, multiple ongoing clinical trials are evaluating the benefit that these changes in lifestyle could have in the oncologic patient (NCT04050397, NCT04507698).

After the 2019 Advanced Prostate Cancer Consensus Conference, there is still no agreement on the duration and treatment scheme with osteoclast-directed therapies in patients with mCRPC. Based on previously published results [71], phase III and IV studies are investigating de-escalation in the treatment frequency of denosumab from four weeks to 12 with the aim of determining possible differences quality of life and SREs in these patients (NCT04549207, NCT02051218).

In patients with CRPC, both second generation hormonal treatments and osteoclast-directed therapies have shown promising results in terms of prevention of metastases or SREs. However, the benefit of the combination of these two types of treatment is still uncertain given the low recruitment of the available clinical trials (NCT03869762). Therefore, there is still a need for further prospective studies that evaluate the synergies of both drugs.

8. Conclusions

The comprehensive management of advanced PCa must include an early evaluation of bone health. We need to carefully evaluate these patients in order to to prevent a high proportion of patients experiencing SREs and subsequent deterioration in quality of life.

Next generation anti-androgens have improved the prognosis of patients with PCa, and together with BPA, delay the onset of SREs and radiological progression in dif-

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ferent scenarios of the disease. In addition to antiresoptive therapies, lifestyle changes and physical exercise seem to benefit these patients.

We must wait for the results of ongoing clinical trials that aim to demonstrate the clinical benefit of the concomitant treatment with BPA and next generation anti-androgens in non metatastatic castration resistant prostate cancer patients.

Author contributions

MAGA, FLC, LPM, DB, JP, XM and JZ—preparation of the manuscript; FLC, FC and MAGA—coordination and final review of the manuscript; ACT, RB, PS and PO—final review of the manuscript.

Ethics approval and consent to participate

Not applicable.

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Conflict of interest

The authors declare no conflict of interest.

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