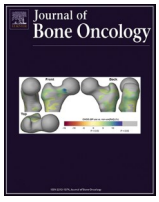
J BONE ONCOL 51 (2025) 100667

Contents lists available at ScienceDirect

Journal of Bone Oncology

journal homepage: www.elsevier.com/locate/jbo



Review

Zoledronic acid in metastatic castrate-sensitive prostate cancer: A state-of-the-art review

Nahed Damaj *, Tala Najdi, Samah Seif, Nicolas Nakouzi, Joseph kattan

Department of Hematology-Oncology, Hôtel Dieu de France Hospital, Faculty of Medicine, Saint- Joseph University of Beirut, Beirut, Lebanon

HIGHLIGHTS

- **Prostate cancer and metastatic disease**: Prostate cancer is the most common cancer in men in developed countries, with metastatic disease to bone causing significant deaths.
- **Androgen Deprivation Therapy (ADT)**: ADT has been the standard treatment for metastatic castration-sensitive prostate cancer (mCSPC), showing clinical responses in most patients.
- **Improved survival with triplet therapy**: Adding docetaxel and androgen receptor pathway inhibitors (ARPI), like abiraterone acetate or darolutamide, to ADT improves overall survival in mCSPC patients, especially those with high-volume disease.
- **Lack of evidence for zoledronic acid**: Despite recent advances, there is limited high-level evidence regarding the addition of zoledronic acid for bone protection in mCSPC patients.
- **Review on zoledronic acid and bone protection agents**: The manuscript reviews the benefits and potential harms of zoledronic acid, alongside exploring alternative bone protecting agents (BPAs) in mCSPC treatment.

ARTICLE INFO

Keywords:
Metastatic castrate sensitive prostate cancer
Bisphosphonates
Zoledronic acid
Bone fracture
Bone metastasis

ABSTRACT

Prostate cancer is the most common cancer in men in developed countries. Despite its slow growing pattern, metastatic disease to bone occurs and results in a significant number of deaths. Since more than eight decades, the classical androgen deprivation therapy (ADT) leads to clinical response in most patients with metastatic castration-sensitive prostate cancer (mCSPC). Moving backward docetaxel and androgen receptor pathway inhibitors (ARPI) from castrate-resistant setting to castrate sensitive setting improves overall survival (OS) compared to ADT alone. Recently, studies suggested that triplet therapy by adding ARPIs such as abiraterone acetate or darolutamide to ADT + docetaxel is more effective than ADT/docetaxel alone in patients with high-volume mCSPC. Although the scientific progress during the last decade, has led to improvements in outcome for patients with mCSPC, there are still several areas impacting daily practice, for which high-level evidence is lacking, especially for adding monthly zoledronic acid in this setting. We structured this review by conducting a comprehensive analysis of the existing literature. This manuscript reviews both the benefits and potential harms of zoledronic acid in the treatment of mCSPC and provides conclusions on the criteria for its use, and the possible use of alternative bone protecting agents (BPA).

1. Introduction

Approximately one in eight American men will be diagnosed with prostate cancer during their lifetime, making it the most common cancer in men after skin cancer [1]. It is estimated that 15 %–17 % of men over age 50 have occult prostate cancer, with this percentage increasing as age advances [2]. Moreover, autopsy studies show that nearly 70 % of men over 80 years old have occult prostate cancer [3]. Although only about one in 41 men will die from prostate cancer, it remains the second leading cause of cancer-related death among American men [1]. Prostate cancer spreads through local extension into the capsule and seminal vesicles, via the lymphatic system to regional lymph nodes, or through the bloodstream to bones and other visceral organs given that bone metastases were found in 90 % of men who had died with metastases of

* Corresponding author at: Department of Hematology-Oncology, Hôtel Dieu de France University Hospital, Beirut, Lebanon.
E-mail address: nahed.damaj@outlook.com (N. Damaj).

https://doi.org/10.1016/j.jbo.2025.100667
Received 10 December 2024; Received in revised form 17 February 2025; Accepted 19 February 2025
Available online 28 February 2025

prostate cancer [4].

Metastatic prostate cancer, either de novo metastatic or relapsing after local therapy, are classically divided in two successive categories: castrate sensitive disease where medical or surgical castration could assume the control, and castrate resistant disease where the disease progressed despite the castration [5].

2. Treatment of metastatic castrate-sensitive prostate cancer

Androgen deprivation therapy (ADT), also known as castration therapy, is the cornerstone of systemic treatment for metastatic prostate cancer either de novo or for relapsed disease [6]. The critical role of androgens in promoting prostate cancer growth was first demonstrated by Huggins and Hodges in the 1940 s, leading to the development of ADT as a standard treatment for advanced prostate cancer. ADT is primarily palliative and results in a decline in prostate-specific antigen (PSA) levels and/or objective tumor responses in over 90 % of patients with advanced prostate cancer [7]. Despite the near-universal initial response to ADT, the duration of effectiveness varies significantly, influenced by various clinical and biological factors. On average, the median time to develop castration resistance or PSA progression while on ADT monotherapy is approximately 7 to 12 months [8]. The objective of ADT, either as surgical castration or medical castration, is to reduce testosterone levels below 50 ng/dL. Surgical castration is achieved through bilateral orchiectomy, while medical castration can be accomplished using either LHRH agonists (such as leuprolide and goserelin) or LHRH antagonists (such as degarelix and relugolix).Both forms of castration are associated with a range of side effects, including impotence, loss of libido, weakness, fatigue, hot flashes, loss of muscle mass, anemia, depression, cardiovascular issues, and a gradual loss of bone density over time [9].

Several clinical trials have explored the intensification of ADT in metastatic castration-sensitive prostate cancer (mCSPC). These trials have investigated the addition of secondary therapies to enhance clinical outcomes and improve overall survival (OS), such as docetaxel chemotherapy or novel hormonal therapies known as ARPI (Androgen Receptor Pathway inhibitors), such as abiraterone acetate, apalutamide, enzalutamide, and darolutamide.

Two randomized controlled trials, the CHAARTED and STAMPEDE (cohorts C) studies, demonstrated improved overall survival (OS) with the addition of six cycles of docetaxel to the ADT backbone [10,11]. Based on these findings, the combination of docetaxel and ADT has become one of the standard treatment regimens for mCSPC. Subgroup analyses of the CHAARTED study, focusing on the "volume" or extent of metastatic disease (high versus low), revealed that the benefit of adding docetaxel is most pronounced in patients with high-volume metastatic disease. High-volume disease was defined as having four or more bone metastases, with at least one lesion located outside the axial skeleton (i.e., skull, ribs, or extremities), or the presence of visceral metastases. Building on the new standard of ADT/docetaxel, the PEACE-1 study, a multicenter European trial, investigated the benefits of adding abiraterone acetate known as the triplet therapy for mCSPC. The results supported the addition of abiraterone to ADT and docetaxel, in high-volume metastatic disease, as recently presented [12]. Also, the ARASENS study confirmed the efficacy of the triplet darolutamide, ADT and docetaxel in an international, placebo-controlled, randomized phase 3 trial [13]. Darolutamide was, thereafter, approved by the FDA in 2022 for use in combination with docetaxel as well as ADT for patients with mCSPC. Interestingly, apalutamide and enzalutamide have both received FDA approval for use associated to ADT for mCSPC treatment [14,15].

The HORRAD and STAMPEDE trials evaluated the efficacy of prostate radiation therapy (RT) in patients with more diffuse metastatic disease treated with ADT alone [6]. Neither trial showed an overall improvement in overall survival (OS) for the entire population. However, in a pre-planned subgroup analysis of the STAMPEDE trial, there was an observed improvement in OS for patients with low-volume metastatic disease. These findings suggest that definitive prostate RT may have a role in the treatment of low volume mCSPC [6].

Thus, nowadays, the standard of care for mCSPC is attributed differently according to the disease volume: it is either the triplet combination of ADT/docetaxel with abiraterone or darolutamide, or ADT plus an ARPI for high volume disease. For low volume mCSPC, it is ADT combined with either an ARPI or radiation therapy (RT) to the prostate.

3. Zoledronic acid as member of the bisphosphonate family

Zoledronic acid is a high potency aminobiphosphonate with osteoclastic inhibiting activity. It is incorporated into the skeleton without being degraded and consequently decreases bone turnover and inhibits of the bone's reparative ability [16].

Zoledronic acid has been approved for prevention and treatment of osteoporosis and glucocorticoids-induced osteoporosis, treatment of Paget's disease, hypercalcemia, multiple myeloma and bone metastasis [17–21]. However, prolonged use of zoledronic acid suppresses bone turnover disabling repair of microdamage [22].

Off-label uses of zoledronic acid include adjuvant therapy in breast cancer, bone loss in postmenopausal patients related to aromatase inhibitor therapy, and bone loss related to androgen deprivation therapy [23].

To explore the use of this molecule in this review, we included recent guidelines, such as the APCCC 2022, ESMO 2020, and the guidelines from Brown, Handforth et al. in JBO 2020. We then incorporated findings from key clinical trials such as STAMPEDE trial. The controversies surrounding the use of zoledronic acid and other treatments in metastatic studies are discussed below.

4. Bone protection for treatment-related bone-loss

Treatment-related bone loss is a well-established concern for patients with prostate cancer (PC) receiving hormonal treatments. ADT can reduce bone mineral density (BMD) by an estimated 2–8 % per year, significantly increasing the risk of fractures due to cancer treatment-induced bone loss [24,25]. Additionally, the addition of ARPIs to ADT may further increase the risk of osteoporotic fractures compared to ADT alone [26,27].

The risk of fractures can be mitigated by using bone-protecting agents (BPAs) like the bisphosphonate zoledronic acid and other alternatives such as the receptor activator of nuclear factor κ B ligand (RANKL) inhibitor denosumab. When BPAs are used in this setting, the interval of administration varies between a few months to one year. Denosumab 60 mg every 6 months, or zoledronic acid 5 mg every 12 months are advised for patients with a dual-energy X-ray absorptiometry (DEXA) T score of <-2.0 and/or at least two of the following risk factors: age >65 years; T score <-1.5; current or former smoker; body mass index <24 kg/m^2; family history of hip fractures; personal history of fragility fractures at age >50 years; or use of oral glucocorticoids for >6 months [28]. Many patients with prostate cancer (PC) meet at least two of the risk criteria for treatment-related bone loss, and as a result, they may not necessarily require a DEXA scan to be eligible for the initiation of BPA therapy. While tools like the Fracture Risk Assessment Tool (FRAX) were not specifically designed for patients on ADT and therefore do not account for cancer treatment-induced bone loss, they can still be valuable for clinicians to assess fracture risk and evaluate individual risk factors.

The current European Association of Urology (EAU) guidelines strongly recommend that patients starting long-term ADT should undergo a baseline DEXA scan to assess BMD. If BPA therapy has not been started, repeat DEXA measurements should be performed every 2 years. For patients with a DEXA T score <-2.5 or additional risk factors that increase annual bone loss by more than 5 %, the EAU guidelines strongly recommend offering BPA therapy such as zoledronic acid 5 mg every

12 months or denosumab 60 mg every 6 months [28].

According to the Advanced Prostate Cancer Consensus Conference (APCCC) 2022 panel members, only 19 % recommended BPA treatment for most mCSPC patients starting ADT in combination with an ARPI. However, this figure increased to 40 % in the APCCC 2024 panel. This shift in opinion may be attributed to recent evidence indicating that the higher fracture risk associated with hormonal therapies often occurs independently of T scores, as ADT not only leads to a quantitative reduction in bone mineral density (BMD) but also causes qualitative changes in bone mass [29,30].

In order to make an informed decision, it is essential to assess fracture risk from baseline, particularly in patients on ADT, including those who have been on ADT for several years or are also undergoing corticosteroid therapy. In the light of this, the guidelines recommend using the FRAX® tool. FRAX® is user-friendly and does not require specialist knowledge, making it suitable for general practice or outpatient settings. It incorporates a limited number of clinical risk factors and it is easy to use [31]. Given that current evidence suggests fracture risk in ADT users is BMD-dependent, it is reasonable to include bone mineral density (BMD) in the FRAX® risk calculation for all prostate cancer patients, wherever feasible. Since newer studies have also shown that ADT not only affects bone mineral density (BMD) but also influences volumetric BMD (vBMD), areal BMD (aBMD), bone microstructure, strength, and body composition. While DXA remains a valuable tool for assessing BMD, the Antelope study suggests that HR-pQCT (high-resolution peripheral quantitative computed tomography) should also be considered as an additional tool for evaluating bone health [32].

5. Zoledronic acid to treat bone metastases in mCSPC

Complications from bone metastases are well known and classified as skeletal-related events (SREs). SREs include bone pain, pathological fractures, the need for radiation therapy (RT) to bone, tumor-related orthopedic surgical interventions, and spinal cord compression. While bone metastases in prostate cancer are primarily osteoblastic, there is also a significant osteolytic component, driven by osteoclast activity. Although pathologic fractures can occur, they are generally less frequent compared to cancers that predominantly feature osteolytic bone disease.

The addition of zoledronic acid, one injection every three to four weeks, is proved effective in term of SREs reduction in metastatic castrate resistant prostate cancer (mCRPC) [33]. Zoledronic acid, approved by the US FDA in 2002 for preventing SREs in men with mCRPC, was tested in a phase 3 trial with 643 patients. The study compared two doses of zoledronic acid (4mgand8mg) to placebo, but switched to a 4 mg dose for all participants due to renal impairment concerns in the higher-dose group. Zoledronic acid significantly reduced SREs (33.2 % vs. 44.2 % for placebo, P = 0.021), delayed the time to first SRE by 167 days, and decreased bone pain during an extended 24-month phase.

However, the efficacy of adding monthly Zoledronic acid, as part of metastatic bone therapy, to the standard doublet or triplet therapy in mCSPC is still not clear. Moreover, specific side effects of monthly Zoledronic acid could exceed its potential benefit in castrate sensitive setting.

6. Controversial results about the use of zoledronic acid in mCSPC

Reports in the literature assessing the added value of monthly zoledronic acid associated to ADT and ARPIs in the castrate sensitive setting are controversial. These findings are summarized in the table below (Table 1).

A post hoc analysis of STAMPEDE data revealed that zoledronic acid, when used as 4 mg every 3 weeks for 6 cycles, then every 4 weeks for 2 years in the hormone-sensitive setting, significantly reduced the risk of fracture-related hospitalizations. Despite the absence of survival benefit from the addition of zoledronic acid, the authors of this analysis concluded that these results support the use of zoledronic acid to decrease fracture risk in patients with mCSPC [34]. The incidence of fractures was high among all patients randomized in the original STAMPEDE trial. Currently, no studies specifically focus on the risk of fracture or potential improvement based on factors in the metastatic setting. For instance, it is debatable whether certain groups of men with metastatic castrate-sensitive prostate cancer (mCSPC) starting ADT could benefit more from bone protective therapy. These groups may include men with osteoporosis or low bone mineral density (BMD) before treatment, older men, particularly those over the age of 70, who are more susceptible to bone density loss, and patients with additional fracture risk factors such as a history of smoking, alcohol use, or low body weight. Furthermore, patients on medications that contribute to bone loss (anticonvulsivants, corticosteroids) could also be candidates for bone-protective agents.

Additionally a key risk factor for bone loss is the duration of ADT, as it is directly linked to decreased bone mineral density, with the most significant effects often observed after 12 months. This makes prolonged ADT a strong justification for the use of bone-protecting agents [35].

In exploring other scenarios that could motivate us for the use of BPA,the CHAARTED trial, which evaluated the addition of docetaxel to ADT in high-volume mCSPC, demonstrated improved survival outcomes. Bone-targeted therapies may help manage SREs in these patients, though specific studies examining the interaction between zoledronic acid and high-volume disease are limited. Since high-volume disease typically involves more extensive bone involvement, bone-targeted therapies are likely more beneficial for managing bone complications in these patients.

Regarding genetic profiles, while germline mutations in genes like BRCA2 and ATM are linked to poorer outcomes in mCSPC and may influence responses to treatments like PARP inhibitors, there is no conclusive evidence connecting these genetic profiles to the effectiveness of zoledronic acid specifically [36]. However, these mutations may increase the risk of bone metastasis, potentially making patients with

Table 1
Studies and their key finding about the use of zoledronic acid in mCSPC.

Study	Population	N	Study groups	Key findings
T.H. Diamond et al study(2001)	Metastatic PC	21	MAB + pamidronate vs MAB	Significant increase in LS (+7.8 % vs −5.7 % p = 0.0001) and femoral neck (+2.0 % vs −2.3 % p = 0.0007) BMD in pamidronate group compared to MAB group
C.W. Ryan et al study (2007)	Localised and metastatic PC receiving ADT < 12 months	42	Zoledronic acid + ADT vs placebo + ADT	Increase in LS (+4.9 % vs − 2.2 % p < 0.0001) and femoral neck (0.9 % vs − 3.2 % p < 0.0001) BMD in zoledronic acid group compared with placebo
STAMPEDE 2023	high-risk, locally advanced, metastatic or recurrent PC	2962	ADT alone vs ADT plus zoledronic acid ADT plus docetaxel vs ADT plus zoledronic acid and docetaxel.	64 % reduction in fracture risk (HR, 0.36; 95 % CI, 0.22–0.57, $P < 0.0005$) in the metastatic setting. No OS improvement
CALGB 90,202 trial (2014)	bone mCSPC on ADT	645	zoledronic acid y vs placebo	No difference in the time to first (SRE) (median 31.9 vs. 29.8 months, HR 0.97) between the two groups. OS not significantly different (median 38 vs. 36 months, HR 0.88, 95 % CI 0.70–1.12).

these profiles more prone SREs, which could further support the use of zoledronic acid or denosumab in these patients.

These scenarios are summarized in the diagram below (Fig. 1).

The guidelines from Brown, Handforth et al. in the 2020 Journal of Bone Oncology (JBO) discuss 15 randomized studies that examined the effects of bisphosphonates and denosumab in men undergoing androgen deprivation therapy (ADT) for prostate cancer. Only two studies reviewed, were in the metastatic setting: C.W. Ryan et al. study and T.H. Diamond et al. with the pamidronate group compared to placebo showed an increase in LS and femoral neck BMD in the zoledronic acid group [37,38].

However, in a multicenter phase II study, patients with de novo or relapsed mCSPC and bone metastases were randomly assigned in a 1:1 ratio to receive either ADT plus enzalutamide (E arm) or the same combination with the addition of monthly zoledronic acid. The primary objective of the study was to evaluate whether the addition of zoledronic acid could significantly increase the bone response rate in the experimental arm after 12 months of treatment, as assessed by whole-body diffusion-weighted magnetic resonance imaging (WB-DW-MRI). WB-DW-MRI scans were conducted centrally at baseline, 6 months, and 12 months, with images being evaluated by the same radiologist for consistency. The conclusion of the study showed that the addition of zoledronic acid to enzalutamide and androgen deprivation therapy (ADT) did not improve bone disease response in patients with mCSPC [39].

In the CALGB 90202 trial, 645 men with bone mCSPC on ADT were randomly assigned to receive either zoledronic acid (4mgintravenouslyevery4weeks) or a placebo. The trial was prematurely discontinued when the corporate sponsor withdrew support [40]. With a median follow-up of 24 months, no statistically significant difference was found in the time to the first skeletal-related event (SRE) (median 31.9 vs. 29.8 months, HR 0.97). Overall survival was also not significantly different between the two groups (median 38 vs. 36 months, HR 0.88, 95 % CI 0.70–1.12).

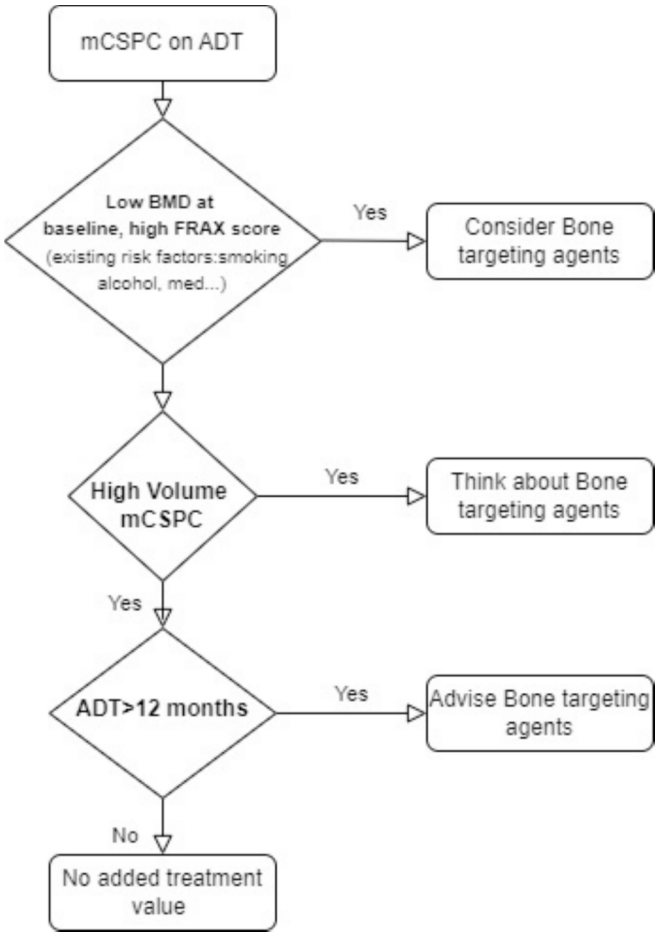


Fig. 1. Diagram illustrating scenarios to take into account when using Bone targeting Agents.

Published guidelines from the Canadian Cancer Society (CCO) and the American Society of Clinical Oncology (ASCO) indicate that there is insufficient evidence to recommend the use of any BPA in men with bone metastases and castration-sensitive prostate cancer [41,42]. Moreover, the 2020 guidelines on bone health from the European Society for Medical Oncology (ESMO) specifically recommend against the routine use of bone-targeted agents, such as Zoledronic acid, in men with metastatic castration-sensitive prostate cancer [26].

In the guidelines from Brown, Handforth et al. in the 2020 Journal of Bone Oncology (JBO), no study was successful to detect differences in fracture incidence.

7. Zoledronic acid toxicities

Zoledronic acid is not an innocent non-toxic drug. It is often associated with an acute-phase reaction within 24 to 72 h following infusion. This reaction typically includes symptoms such as low-grade fever, myalgias, and arthralgias [43]. One potential side effect is hypocalcemia, a transient drop in calcium levels, which is more likely to occur in patients with hypoparathyroidism, vitamin D deficiency, or inadequate calcium intake [44,45]. Calcium levels should be closely monitored, particularly before beginning treatment and during the first few weeks afterward. Supplementation may be necessary. Bone health guidelines recommend daily supplements (800–2000 IU per day) of vitamin D3 and a daily intake of 1000–1200 mg of calcium per day. (bone health in cancer esmo) The calcium and vitamin D supplements should not be taken within one hour of bisphosphonate administration, as they can interfere with absorption.

In rare cases, patients may experience severe musculoskeletal pain in the bones, joints, or muscles, which can persist for days, months, or even years after starting bisphosphonate therapy [46]. Additionally, impaired kidney function is a concern. During bone therapy, the risk of nephropathy can be minimized by avoiding nephrotoxic drugs and products, monitoring baseline creatinine levels, and progressively reducing the dose when baseline creatinine clearance is between 30–60 ml/min. Zoledronate is contraindicated for patients with a creatinine clearance of less than 30 ml/min.

Another rare but serious complication is osteonecrosis of the jaw (ONJ). The frequency of ONJ according to the literature is around 1.2–3.8 % [47], but when it occurs, it is always severe disturbing the quality of life and rarely reversible according to our daily practice. Moreover, ONJ can occur with any bisphosphonate use, especially in patients receiving long-term treatment for osteoporosis [48]. A good oral hygiene is highly recommended. To prevent the risk of ONJ, patients are advised a scheduled regular or oral check-ups, invasive dental procedures such as implants or extractions should be avoided during the period of treatment if possible. Lastly, long-term bisphosphonate use has been linked to atypical femur fractures, particularly with prolonged use beyond three to five years, in older adults (ages 65–84), those on glucocorticoids, shorter individuals, those with higher weight, and Asian Americans compared to White Americans [49]. A referral for a supervised exercise program for a minimum of 12 weeks is suggested.

8. Other alternatives BPA

In castration-resistant prostate cancer (CRPC), denosumab has been shown to delay the time to the first skeletal-related event (SRE) and result in an 18 % reduction in cumulative SREs compared to zoledronate. Additionally, denosumab has been observed to delay the need for analgesics [26,50].

When comparing toxicities of other BPA (denosumab and pamidronate) with zoledronic acid, these agents generally present similar adverse effects, although electrolyte levels should be more closely monitored. In a recent *meta*-analysis by Chen et al., an increased occurrence of hypocalcemia and osteonecrosis of the jaw (ONJ) was observed with denosumab compared to zoledronic acid [51]. However, denosumab demonstrated a significantly lower incidence of renal adverse events and acute phase reactions, making it the preferred treatment in patients with low creatinine levels. Additionally, denosumab appears to delay the need for analgesics more effectively than zoledronic acid. Cost-wise, however, zoledronic acid remains a more affordable option [52].

9. Conclusion

Bone involvement is common in metastatic hormone-sensitive prostate cancer (mHSPC). ADT remains the cornerstone of systemic treatment for metastatic prostate cancer. For all patients undergoing long-term ADT, it is recommended to take calcium and vitamin D supplements, engage in regular exercise, quit smoking, and limit alcohol intake to reduce the risk of treatment induced bone-loss. In fact, all patients receiving continuous hormonal therapy should be evaluated for potential bone-protecting agent therapy. A baseline dual-energy X-ray absorptiometry (DEXA) scan should be performed to assess BMD, with repeat scans every 2 years if antiresorptive therapy has not been initiated. Denosumab 60 mg every 6 months, or zoledronic acid 5 mg every 12 months could be used as BPA in this setting.

For men with bone metastases and castration-sensitive prostate cancer, although some studies have shown benefits in maintaining bone mineral density with the use of these agents, no solid evidence suggested an improvement in incidence of fractures among patients taking BPA. Oncologists should be aware that the use of monthly zoledronic acid for preventing or delaying complications from bone metastases. is not encouraged in the absence of other arguments supporting its use such as low bone mineral density, other risk factors of fractures or a long duration on ADT. Moreover, any potential advantage in this setting from adding zoledronic acid could be uncompensated by its toxicities. While some of these toxicities can be mitigated by using other molecules, such as anti-RANK agents, other toxicities remain common across all bone protecting agents.

CRediT authorship contribution statement

Nahed Damaj: Writing – review & editing, Writing – original draft, Visualization, Software, Resources, Project administration, Data curation. **Tala Najdi:** Data curation. **Samah Seif:** Conceptualization. **Nicolas Nakouzi:** Data curation. **Joseph kattan:** Visualization, Validation, Supervision.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Nahed Damaj reports a relationship with Saint Joseph University of Beirut that includes. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] I.M. Thompson, P.J. Goodman, C.M. Tangen, M.S. Lucia, G.J. Miller, L.G. Ford, et al., The influence of finasteride on the development of prostate cancer, N. Engl. J. Med. 349 (3) (2003) 215–224.

[2] N.B. Delongchamps, A. Singh, G.P. Haas, The role of prevalence in the diagnosis of prostate cancer, Cancer Control 13 (3) (2006) 158–168.

[3] L.A. Mucci, J.B. Hjelmborg, J.R. Harris, K. Czene, D.J. Havelick, T. Scheike, et al., Familial risk and heritability of cancer among twins in Nordic countries, J. Am. Med. Assoc. 315 (1) (2016) 68–76.

[4] L. Bubendorf, A. Schöpfer, U. Wagner, G. Sauter, H. Moch, N. Willi, et al., Metastatic patterns of prostate cancer: an autopsy study of 1,589 patients, Hum. Pathol. 31 (5) (2000) 578–583.

[5] Scher HI, Halabi S, Tannock I, Morris M, Sternberg CN, Carducci MA, et al. Design and End Points of Clinical Trials for Patients With Progressive Prostate Cancer and Castrate Levels of Testosterone: Recommendations of the Prostate Cancer Clinical Trials Working Group. JCO. 2008;26(7):1148–59.

[6] R.Z. Szmulewitz, C.J. Peer, A. Ibraheem, E. Martinez, M.F. Kozloff, B. Carthon, et al., Prospective international randomized phase II study of low-dose abiraterone with food versus standard dose abiraterone in castration-resistant prostate cancer, J. Clin. Oncol. 36 (14) (2018) 1389–1395.

[7] A randomized phase II cross-over study of abiraterone + prednisone (ABI) vs enzalutamide (ENZ) for patients (pts) with metastatic, castration-resistant prostate cancer (mCRPC). | Request PDF [Internet]. [cited 2025 Feb 15]. Available from: https://www.researchgate.net/publication/345634690_A_randomized_phase_II_cross-over_study_of_abiraterone_prednisone_ABI_vs_enzalutamide_ENZ_for_patients_pts_with_metastatic_castration-resistant_prostate_cancer_mCRPC.

[8] A.J. Armstrong, S. Halabi, J. Luo, D.M. Nanus, P. Giannakakou, R.Z. Szmulewitz, et al., Prospective multicenter validation of androgen receptor splice variant 7 and hormone therapy resistance in high-risk castration-resistant prostate cancer: the PROPHECY study, J. Clin. Oncol. 37 (13) (2019) 1120–1129.

[9] M. Eisenberger, A.C. Hardy-Bessard, C.S. Kim, L. Géczi, D. Ford, L. Mourey, et al., Phase III study comparing a reduced dose of cabazitaxel (20 mg/m2) and the currently approved dose (25 mg/m2) in postdocetaxel patients with metastatic castration-resistant prostate cancer-PROSELICA, J. Clin. Oncol. 35 (28) (2017) 3198–3206.

[10] M.R. Sydes, M.R. Spears, M.D. Mason, N.W. Clarke, D.P. Dearnaley, J.S. de Bono, et al., Adding abiraterone or docetaxel to long-term hormone therapy for prostate cancer: directly randomised data from the STAMPEDE multi-arm, multi-stage platform protocol, Ann. Oncol. 29 (5) (2018) 1235–1248.

[11] C.E. Kyriakopoulos, Y.H. Chen, M.A. Carducci, G. Liu, D.F. Jarrard, N.M. Hahn, et al., Chemohormonal therapy in metastatic hormone-sensitive prostate cancer: long-term survival analysis of the randomized phase III E3805 CHAARTED Trial, J. Clin. Oncol. 36 (11) (2018) 1080–1087.

[12] N.D. James, N.W. Clarke, A. Cook, A. Ali, A.P. Hoyle, G. Attard, et al., Abiraterone acetate plus prednisolone for metastatic patients starting hormone therapy: 5-year follow-up results from the STAMPEDE randomised trial (NCT00268476), Int. J. Cancer 151 (3) (2022) 422–434.

[13] M.R. Smith, M. Hussain, F. Saad, K. Fizazi, C.N. Sternberg, E.D. Crawford, et al., Darolutamide and survival in metastatic, hormone-sensitive prostate cancer, N. Engl. J. Med. 386 (12) (2022) 1132–1142.

[14] ERLEADA® (apalutamide) demonstrates statistically significant and clinically meaningful improvement in overall survival compared to enzalutamide in patients with metastatic castration-sensitive prostate cancer [Internet]. [cited 2025 Feb 15]. Available from: https://www.jnj.com/media-center/press-releases/erleada-apalutamide-demonstrates-statistically-significant-and-clinically-meaningful-improvement-in-overall-survival-compared-to-enzalutamide-in-patients-with-metastatic-castration-sensitive-prostate-cancer.

[15] Clarke H. Apalutamide associated with improved 2-year survival vs enzalutamide in mCSPC. 2024 Oct 2 [cited 2025 Feb 15];53. Available from: https://www.urologytimes.com/view/apalutamide-associated-with-improved-survival-vs-enzalutamide-in-mcspc.

[16] G.A. Rodan, A.A. Reszka, Bisphosphonate mechanism of action, Curr. Mol. Med. 2 (6) (2002) 571–577.

[17] T. Mashiba, S. Mori, D.B. Burr, S. Komatsubara, Y. Cao, T. Manabe, et al., The effects of suppressed bone remodeling by bisphosphonates on microdamage accumulation and degree of mineralization in the cortical bone of dog rib, J. Bone Miner. Metab. 23 (Suppl) (2005) 36–42.

[18] R. von Moos, C. Sternberg, J.J. Body, C. Bokemeyer, Reducing the burden of bone metastases: current concepts and treatment options, Support Care Cancer 21 (6) (2013) 1773–1783.

[19] P. Chotiyarnwong, E.V. McCloskey, Pathogenesis of glucocorticoid-induced osteoporosis and options for treatment, Nat. Rev. Endocrinol. 16 (8) (2020) 437–447.

[20] Qaseem A, Forciea MA, McLean RM, Denberg TD, Clinical Guidelines Committee of the American College of Physicians, Barry MJ, et al. Treatment of Low Bone Density or Osteoporosis to Prevent Fractures in Men and Women: A Clinical Practice Guideline Update From the American College of Physicians. Ann Intern Med. 2017;166(11):818–39.

[21] K. Anderson, N. Ismaila, P.J. Flynn, S. Halabi, S. Jagannath, M.S. Ogaily, et al., Role of bone-modifying agents in multiple myeloma: American society of clinical oncology clinical practice guideline update, J. Clin. Oncol. 36 (8) (2018) 812–818.

[22] M. Pineda-Moncusí, N. Garcia-Giralt, A. Diez-Perez, S. Servitja, I. Tusquets, D. Prieto-Alhambra, et al., Increased fracture risk in women treated with aromatase inhibitors versus tamoxifen: beneficial effect of bisphosphonates, J. Bone Miner. Res. 35 (2) (2020) 291–297.

[23] Canadian Urological Association guideline on androgen deprivation therapy: Adverse events and management strategies - PubMed [Internet]. [cited 2025 Feb 15]. Available from: https://pubmed.ncbi.nlm.nih.gov/34127184/.

[24] Maximal androgen blockade therapy (MAB) for prostate cancer (PC) and risk of bone fractures: A systematic literature review and meta-analysis. | Request PDF [Internet]. [cited 2025 Feb 15]. Available from: https://www.researchgate.net/publication/381238043_Maximal_androgen_blockade_therapy_MAB_for_prostate_

cancer_PC_and_risk_of_bone_fractures_A_systematic_literature_review_and_meta-analysis.
[25] F. Turco, L. Di Prima, C. Pisano, S. Poletto, M. De Filippis, V. Crespi, et al., How to improve the quality of life of patients with prostate cancer treated with hormone therapy? Res Rep Urol. 15 (2023) 9–26.
[26] R. Coleman, P. Hadji, J.J. Body, D. Santini, E. Chow, E. Terpos, et al., Bone health in cancer: ESMO clinical practice guidelines†, Ann. Oncol. 31 (12) (2020) 1650–1663.
[27] F. Turco, S. Gillessen, G. Treglia, K. Fizazi, M.R. Smith, B. Tombal, et al., Safety profile of darolutamide versus placebo: a systematic review and meta-analysis, Prostate Cancer Prostatic Dis. 27 (3) (2024) 385–392.
[28] D. Tilki, R.C.N. van den Bergh, E. Briers, T. Van den Broeck, O. Brunckhorst, J. Darraugh, et al., EAU-EANM-ESTRO-ESUR-ISUP-SIOG Guidelines on prostate cancer. Part II-2024 update: treatment of relapsing and metastatic prostate cancer, Eur. Urol. 86 (2) (2024) 164–182.
[29] S.L. Greenspan, J. Wagner, J.B. Nelson, S. Perera, C. Britton, N.M. Resnick, Vertebral fractures and trabecular microstructure in men with prostate cancer on androgen deprivation therapy, J. Bone Miner. Res. 28 (2) (2013) 325–332.
[30] F. Turco, M. Tucci, C. Buttigliero, Adverse event assessment in prostate cancer patients receiving androgen deprivation therapy: are we doing enough? Minerva Urol Nephrol. 73 (6) (2021) 870–872.
[31] J.E. Brown, C. Handforth, J.E. Compston, W. Cross, N. Parr, P. Selby, et al., Guidance for the assessment and management of prostate cancer treatment-induced bone loss. A consensus position statement from an expert group, J. Bone Oncol. 1 (25) (2020) 100311.
[32] C. Handforth, M.A. Paggiosi, R. Jacques, F. Gossiel, R. Eastell, J.S. Walsh, et al., The impact of androgen deprivation therapy on bone microarchitecture in men with prostate cancer: a longitudinal observational study (The ANTELOPE Study), J. Bone Oncol. 47 (2024) 100611.
[33] F. Saad, D.M. Gleason, R. Murray, S. Tchekmedyian, P. Venner, L. Lacombe, et al., A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma, J. Natl. Cancer Inst. 94 (19) (2002) 1458–1468.
[34] C. Jones, P. Dutey-Magni, L.R. Murphy, M. Murray, J.E. Brown, E. McCloskey, et al., 1768MO Incidence of fracture related hospitalisations in men with de novo high risk localised and metastatic hormone sensitive prostate cancer: analysis of routinely collected healthcare data from the STAMPEDE docetaxel and zoledronic acid comparisons, Ann. Oncol. 1 (34) (2023) S956–S957.
[35] M. Bienz, F. Saad, Androgen-deprivation therapy and bone loss in prostate cancer patients: a clinical review, Bonekey Rep. 4 (2015) 716.
[36] J. Hwang, X. Shi, A. Elliott, T.E. Arnoff, J. McGrath, J. Xiu, et al., Metastatic prostate cancers with BRCA2 versus ATM mutations exhibit divergent molecular features and clinical outcomes, Clin. Cancer Res. 29 (14) (2023) 2702–2713.
[37] T.H. Diamond, J. Winters, A. Smith, P. De Souza, J.H. Kersley, W.J. Lynch, et al., The antiosteoporotic efficacy of intravenous pamidronate in men with prostate carcinoma receiving combined androgen blockade: a double blind, randomized, placebo-controlled crossover study, Cancer 92 (6) (2001) 1444–1450.
[38] C.W. Ryan, D. Huo, K. Bylow, L.M. Demers, W.M. Stadler, T.O. Henderson, et al., Suppression of bone density loss and bone turnover in patients with hormone-sensitive prostate cancer and receiving zoledronic acid, BJU Int. 100 (1) (2007) 70–75.
[39] A. Dalla Volta, F. Valcamonico, A. Zivi, G. Procopio, P. Sepe, G. Del Conte, et al., Whole-body diffusion-weighted magnetic resonance imaging to assess bone response in patients with hormone-sensitive metastatic prostate cancer randomly assigned to receive androgen deprivation + enzalutamide ± zoledronic acid, JCO 41 (6_suppl) (2023) 46.
[40] M.R. Smith, S. Halabi, C.J. Ryan, A. Hussain, N. Vogelzang, W. Stadler, et al., Randomized controlled trial of early zoledronic acid in men with castration-sensitive prostate cancer and bone metastases: results of CALGB 90202 (alliance), J. Clin. Oncol. 32 (11) (2014) 1143–1150.
[41] P.J. Saylor, R.B. Rumble, S. Tagawa, J.A. Eastham, A. Finelli, P.S. Reddy, et al., Bone health and bone-targeted therapies for prostate cancer: ASCO endorsement of a cancer care Ontario guideline, JCO 38 (15) (2020) 1736–1743.
[42] S.M.H. Alibhai, K. Zukotynski, C. Walker-Dilks, Bone health and bone-targeted therapies for nonmetastatic prostate cancer, Ann. Intern. Med. 168 (6) (2018) 459–460.
[43] D.M. Black, P.D. Delmas, R. Eastell, I.R. Reid, S. Boonen, J.A. Cauley, et al., Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis, N. Engl. J. Med. 356 (18) (2007) 1809–1822.
[44] D.H. Schussheim, T.P. Jacobs, S.J. Silverberg, Hypocalcemia associated with alendronate, Ann. Intern. Med. 130 (4 Pt 1) (1999) 329.
[45] C.J. Rosen, S. Brown, Severe hypocalcemia after intravenous bisphosphonate therapy in occult vitamin D deficiency, N. Engl. J. Med. 348 (15) (2003) 1503–1504.
[46] D.K. Wysowski, J.T. Chang, Alendronate and risedronate: reports of severe bone, joint, and muscle pain, Arch. Intern. Med. 165 (3) (2005) 346–347.
[47] H.R. Kourie, J. Antoun, E. El Rassy, M. Rassy, C. Sader-Ghorra, J. Kattan, Osteonecrosis of the jaw during biyearly treatment with zoledronic acid for aromatase inhibitor associated bone loss in early breast cancer: a literature review, J Bone Oncol. 4 (3) (2015) 77–79.
[48] R.A. Adler, G. El-Hajj Fuleihan, D.C. Bauer, P.M. Camacho, B.L. Clarke, G.A. Clines, et al., Managing osteoporosis in patients on long-term bisphosphonate treatment: report of a task force of the AMERICAN society for bone and mineral research, J. Bone Miner. Res. 31 (1) (2016) 16–35.
[49] E. Shane, D. Burr, P.R. Ebeling, B. Abrahamsen, R.A. Adler, T.D. Brown, et al., Atypical subtrochanteric and diaphyseal femoral fractures: report of a task force of the American Society for Bone and Mineral Research, J. Bone Miner. Res. 25 (11) (2010) 2267–2294.
[50] R. von Moos, L. Costa, E. Gonzalez-Suarez, E. Terpos, D. Niepel, J.J. Body, Management of bone health in solid tumours: from bisphosphonates to a monoclonal antibody, Cancer Treat. Rev. 76 (2019) 57–67.
[51] L. Sun, S. Yu, Efficacy and safety of denosumab versus zoledronic acid in patients with bone metastases: a systematic review and meta-analysis, Am. J. Clin. Oncol. 36 (4) (2013) 399–403.
[52] V. Mollica, G. Nuvola, E. Tassinari, M.C. Nigro, A. Marchetti, M. Rosellini, et al., Bone targeting agents in patients with prostate cancer: general toxicities and osteonecrosis of the jaw, Curr. Oncol. 29 (3) (2022) 1709–1722.