Practical guide to bone health in the spectrum of advanced prostate cancer

Valentina Butoescu, MD, Bertrand Tombal, MD
Cliniques universitaires Saint-Luc, Institut de Recherche Clinique Université catholique de Louvain, Brussels, Belgium

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Introduction: *In the advanced stage of prostate cancer, bone is consistently the first and, later on, the dominant extra-nodal metastatic site. Bone metastases account for most of prostate cancer's morbidity.*
Materials and methods: *We have performed a literature review using the MEDLINE database for publications on: 1) bone metastases (androgen deprivation therapy); 2) cancer treatment induce bone loss; 3) skeletal related events; 4) denosumab; 5) zoledronic acid.*
Results: *Prostate cancer cells disrupt the normal bone remodeling process, invade the skeletal environment, and ultimately weaken the bone structure. This may result in skeletal complications, also known as skeletal related events (SREs), including pain, fractures, spinal cord compressions requiring surgery, radiotherapy or change in anti-cancer treatments. SREs negatively impact quality-of-life and survival and represent a major cost for the healthcare system. The bone metastases conundrum is further aggravated by the fact that androgen deprivation therapy (ADT), the reference systemic treatment of advanced prostate cancer, profoundly affects the skeletal integrity as well. ADT accelerates the physiological bone resorption, leading to osteoporosis and fragility fractures.*
Conclusion: *The concept of "bone health" or "skeletal heath" refers to the diagnostic, prevention, and treatment of cancer treatment induced bone loss (CTIBL) and metastasis, and their respective complications, osteoporotic fractures and SREs.*

Key Words: prostate cancer, androgen deprivation therapy, osteoporosis, skeletal related events, bisphosphonates, denosumab

Introduction

Advanced prostate cancer is characterized by a very high tropism to bone.[1,2] Less than 10% of men diagnosed with prostate cancer will ultimately die of the disease.[3] In those progressing to lethal stage prostate cancer, the skeleton is the first metastatic extra-nodal landing site in 80% of patients and, overall, 90% of patients will have bone metastases.[4,5] The metastatic tissue replaces the normal bone marrow content, leading to anemia. But more importantly, metastases alter the normal bone remodeling processes and invade the surrounding structures, resulting in complications such as pathologic fractures, pain, spinal cord compression. Registration authorities have aggregated these complications and coined the term of skeletal-related events (SREs), mostly for the purpose of proper evaluation of new pharmacological entities.[6] SREs are common in all "osteotropic" cancers, such as breast, prostate, and lung cancer.

In breast and prostate cancer, skeletal integrity is also compromised by hormonal treatments, androgen deprivation therapy (ADT) in prostate cancer patients. ADT increases bone resorption and is a known risk factor for osteoporosis and osteoporotic fractures.

The concept of "bone health" or "skeletal heath" refers to the diagnostic, primary and pharmacological prevention, and treatment of cancer treatment induced bone loss (CTIBL) and metastasis, and their respective complications, osteoporotic fractures and SREs. Bone health is a major issue in prostate cancer because it impacts quality and duration of life of the patients. The

Address correspondence to Dr. Bertrand Tombal, Service d'Urologie, Cliniques universitaires Saint Luc, Avenue Hippocrate, 10, B-1200 Brussels, Belgium

TABLE 1. **Observed changes in bone mineral density at 12 months in patients treated with androgen deprivation therapy**

Study	Patient number	Treatment	BMD changes at 12 months
Eriksson et al[7]	27	Orchiectomy or oestrogens	Hip: -9.6% Radius: -4.5%
Maillefert et al[8]	12	LHRH agonist	Hip: -3.9% Lumbar spine: -4.6%
Daniell et al[10]	235	Orchiectomy or LHRH agonist	Hip: -2.4%
Berrutti et al[50]	35	LHRH agonist	Hip: -0.6% Lumbar spine: -2.3%
*Higano et al[51]	19	LHRH agonist	Hip: -2.7% Lumbar spine: -4.7%
Mittan et al[13]	15	LHRH agonist	Hip: -3.3% Radius: -5.3%

*9 months of androgen deprivation therapy
BMD = bone mineral density; LHRH = luteinizing hormone releasing hormone

aim of this review is to understand the basic facts and figures of CTIBL and bone metastasis and to provide some guidance on when and how to administer preventive or curative measures. This review will not include information on recent developments in diagnostic techniques or data on radionuclides.

ADT induced CTIBL in prostate cancer patients

The association between surgical castration and accelerated bone loss was first described more than 15 years ago and confirmed since then by several prospective studies.[7-12] After 12 months of ADT, men would usually lose between 2% and 10% of their bone mineral density (BMD), measured by dual-energy x-ray absorptiometry (DXA) at their hip or radius, Table 1. CTIBL begins very early in the course of treatment with ADT, as suggested by the concentration of urinary bone resorption marker N-telopeptide that already increases after 6 months of ADT.[13] Large epidemiological surveys have demonstrated that ADT induced CTIBL increases the risk of fragility fracture, modestly but significantly, Table 2.[14-16] This risk may although become significant when added to other traditional risk factors such as a low or high body mass index, a history of a prior fracture at more than 50 years of age, a parental history of hip fracture, being a current smoker, receiving corticosteroid treatment for > 3 months, an excessive alcohol use, and a history of rheumatoid arthritis.[17] These additional risk factors are important to decide if a patient requires treatment. In addition, the impact of ADT should be modulated according to the age of the patient and the duration of treatment. In one of the aforementioned surveys, the relative risk of any fracture was 1.07 for patients receiving ≤ 4 monthly doses of luteinizing hormone releasing hormone (LHRH) agonists and 1.45 for ≥ 9 doses, the relative risk increasing by 1.21 for each age 5 year categories.[15]

TABLE 2. **Risk of fracture associated with chronic administration of androgen deprivation therapy (ADT)**

Study	Patient number	ADT duration	Fracture risk (%)					
			All sites		Hip		Hospitalization	
			ADT	No ADT	ADT	No ADT	ADT	No ADT
Shahinian et al[15]	50613	1 yr-5 yr	19.6	12.6	4.06	2.06	5.19	2.37
Smith et al[16]	11661	> 12 yr	7.88*¶	6.51*¶	1.26*	0.98*		
Alibhai et al[14]	19079	6.7 yr	17.2¶¶	12.7¶¶	2.6	2	8	5.7

*rate per 100 person-years; ¶relative risk 1.21; p < 0.001 ¶¶hazard ratio 1.65, 95% CI 1.53-1.78

Monitoring and prevention of CTIBL in ADT treated patients

DXA can be used to monitor spine, hip, or total body BMD. The spine is the preferred site of densitometry for serial measurement of bone mass to monitor changes in BMD.[18] The European Association of Urology (EAU) guidelines recommend performing a DXA every 2 years after initiation of castration, provided there are no other risk factors, and every year if there are risk factors.[19] Patients should be encouraged to make specific lifestyle changes: quit smoking, reduce alcohol and caffeine consumption, engage in regular weight-bearing exercises, and favor a healthy diet of foods and beverages containing calcium (dairy) and vitamin D (fatty fish).[20] The National Comprehensive Cancer Network (NCCN) guidelines recommend assessing fracture risk using the FRAX algorithm (www.shef.ac.uk/FRAX/index.htm) by considering CTIBL as "secondary osteoporosis".[21]

Pharmacological prevention and treatment of ADT induced CTIBL

One of the most important questions for the physicians is when to initiate preventive treatment in ADT treated patients.

Physicians should make the difference between osteopenia and osteoporosis. This can be evaluated using the T-score on DXA and the WHO classification. The T-score is the number of standard deviations above or below the mean for a healthy 30-year-old adult of the same sex and ethnicity as the patient. Osteopenia is defined by a T score <-1 and >-2.5; osteoporosis by a T score ≤ -2.5, and severe osteoporosis by a T score ≤ -2.5 with history of 1 or more fragility fracture. Osteoporosis is a condition that must be corrected notwithstanding initiation of ADT. The question is more about the benefit of treating osteopenic patients before they are really osteoporotic, as an alternative to monitor BMD during ADT.

The EAU guidelines recommend treating osteoporotic patients (DXA T-score ≤ -2.5) with denosumab or bisphosphonates, but provide no guidance for osteopenic patients.[19] NCCN guidelines recommend treatment with zoledronic acid (ZA) (5 mg IV annually), alendronate (70 mg PO weekly), or denosumab (60 mg sc every 6 months) for men with a 10 year probability of hip fracture ≥ 3% or a 10 year probability of major osteoporosis-related fracture ≥ 20% on the FRAX algorithm.[21]

Denosumab (denosumabis) a fully human monoclonal antibody that specifically inhibits the receptor activator of nuclear factor-KB (RANK) ligand (RANKL), which is produced by osteoblasts and progenitor cells and plays a central role in the maturation of pre-osteoclasts into osteoclasts.[22] Denosumab, administered subcutaneously (sc) every 6 months at the dose of 60 mg, is currently the only agent approved by Food and Drug Administration (FDA) and European Medicines Agency (EMA) for the prevention of osteoporotic facture in non-metastatic ADT treated patients. Inclusion criteria of the registration trial were: ≥ 70 years old, or a DXA T-score <–1.0 at baseline, or a history of osteoporotic fracture.[23] These criteria actually describe a mixed population of osteopenic and osteoporotic patients. In the registration trial, denosumab significantly increased BMD and decreased the incidence of new vertebral fractures at 36 months (1.5% versus 3.9% with placebo; p = 0.006).[23] In that setting, the incidence of side effects was low.

Although not registered for that specific indication, bisphosphonates zoledronic acid (4 mg IV every 3 or 12 months) and alendronate (90 mg oral weekly) have been studied in that indication, in smaller shorter studies not powered to detect a reduction of the incidence of fracture, Figure 1.[24-26] Although recommended by guidelines, prescription of bisphosphonates in osteopenic patients not supported by specific registration should be left to the discretion of the physician.[19]

Prevention of complications of bone metastases

With the widespread use of prostate-specific antigen (PSA), most patients are diagnosed with localized or locally advanced disease and ADT is usually started in absence of any radiological evidence of metastases. Similarly, most patients will progress and become resistant to castration with no detectable metastasis.[27] But ultimately, the skeleton will be the first metastatic site in 80% of patients and, later on, 90% of patients will have bone metastases.[4,5]

Prostate cancer cells disseminating in the bone marrow do not destroy the bone on their own. Instead, they alter the functions of osteoclasts and osteoblasts, and hijack signals coming from the bone matrix, thereby disrupting physiological bone remodeling.[28] Specifically, there is a 'vicious cycle' whereby metastatic cells residing in the bone marrow secrete factors that stimulate osteoclast-mediated bone resorption whereas growth factors released from resorbed bone stimulate tumor growth. Taken together, this leads to an imbalance between bone resorption and bone formation, resulting in enhanced skeletal destruction and occurrence of SREs.[29] SREs are present at diagnosis of bone metastasis in 10% of

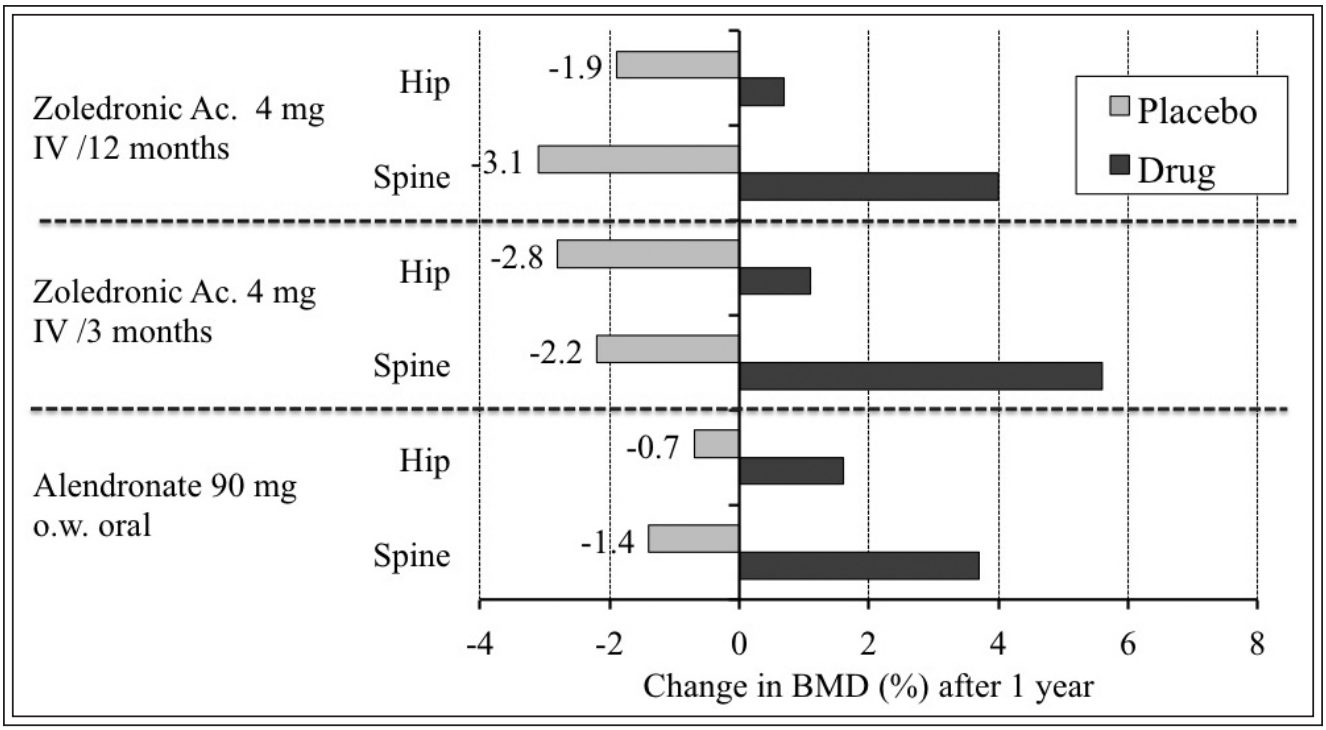

Figure 1. Benefit of bisphosphonate of prevention of androgen deprivation therapy induced cancer treatment induced bone loss in prostate cancer patients.

prostate cancer patients. Later on, 50% of bone metastatic castration resistant prostate cancer (CRPC) patients will experience one or more SREs.[30,31] In the ZA registration trial, the mean annual incidence of SREs in the placebo group was 1.47.[32] The presence of SREs is significantly associated with worse survival, poorer quality-of-life in CRPC patients, and a significant cost for the healthcare system.[33,34]

Pharmacological prevention of SREs, Table 3

The bisphosphonates clodronate and pamidronate were tested against placebo in three trials with palliative endpoints, both failing to provide significant clinical benefit, explaining why these drugs have never been widely prescribed by urologists in metastatic patients. Triweekly clodronate (intravenous (IV) 1500 mg) has

TABLE 3. **Summary of studies evaluating bone targeted agents in the prevention of SRE in bone metastatic CRPC patients**

Drugs	**Pamidronate versus placebo[36]**	**Zoledronate versus placebo[32]**	**Denosumab versus zoledronate[31]**
Number of patients	320	422	1701
Study duration	Fixed at 27 weeks	Fixed at 24 months	Event-driven, maximum 41 months treatment
% patients with SRE (p)	25 versus 25 (NR)	38 versus 49 (0.009)	36 versus 41
Median time to first on-study SRE (months)	Not tested	16.0 versus 10.5; p = 0.009	20.7 versus 17.1 p = 0.0002 non-inferiority, 0.008 superiority
Benefit on time to first and subsequent SREs	Not tested	HR = 0.64; p = 0.002	HR = 0.82; p = 0.008

SRE = skeletal related event; CRPC = castration resistant prostate cancer; HR = hazard ratio

been tested in a randomized controlled trial (RCT) on 209 symptomatic bone metastatic CRPC patients scheduled to receive mitoxantrone and prednisone.[35] There was no difference in palliative response, symptomatic progression free survival (PFS), overall survival (OS), and health related quality-of-life (HRQoL).

Triweekly pamidronate (IV 90 mg) has been tested in two similarly designed RCTs on a total of 378 symptomatic CRPC patients.[36] The pooled analysis did not detect significant differences in self-reported pain score, analgesic use, incidence of SREs, and mobility between pamidronate and placebo.

Zoledronic acid (ZA) was the first bisphosphonate to be approved for the prevention of SREs in bone metastatic CRPC. The 3 arms randomized controlled registration trial compared triweekly ZA IV, at a dose of 4 mg or 8 mg or placebo for 15 months.[32] The endpoints included proportion of patients with SREs, time to first SRE, skeletal morbidity rate, pain and analgesic scores, and disease progression. Excessive nephrotoxicity lead to a dose-reduction to 4 mg in the 8 mg treatment arm and to an increase in the infusion time from 5 minutes to 15 minutes. At the dose of 4 mg, ZA reduced the incidence of SREs by 11% compared to placebo (44.2% versus 33.2%; p = 0.021).[37] In the long term report, the median time to the first on-study SRE was 488 days for the ZA 4 mg versus 321 days for the placebo (p = 0.009); the annual incidence of SREs was 0.77 with ZA versus 1.47 with placebo (p = 0.005).[32] The study failed to show an OS improvement, although there was a trend toward a longer survival in patients receiving ZA (546 days versus 469 days for placebo; p = 0.103).[38]

Denosumab has been developed for the prevention of SRE in various cancer types at the monthly dose of 120 mg sc, 12 times higher than the dose used in osteoporosis treatment. The dose was optimized to achieve sustained suppression of bone markers; patients on less frequent dosing schedules showing evidence of escape.[39] Denosumab has been directly compared to monthly ZA (4 mg IV) in 1904 bone metastatic CRPC patients.[31] The primary endpoint was time to first on-study SRE and was assessed for non-inferiority. Secondary endpoints included assessment for superiority in time to first SRE and OS. Denosumab delayed by 18% the time to the first on-study SRE (20.7 months denosumab versus 17.1 months ZA, HR = 0.82, 95% CI 0.71-0.95; p = 0.0002 for non-inferiority and 0.008 for superiority). Denosumab also significantly delayed the time to first and subsequent SRE and reduced the total number of SRE observed in the trial (494 with denosumab versus 584 with ZA). There was no difference in OS and time to disease progression.

The impact of ZA and denosumab on pain and HRQoL has been also documented. In the ZA registration trial, mean least-squares in the bone pain index (BPI) change from baseline value at 18 months was 0.58 for ZA and 0.95 for placebo (p = 0.075); at 24 months it was 0.58 and 1.07 (p = 0.024), respectively.[32] The additional benefit of denosumab over ZA has been measured on a denosumab pooled analysis of the three similar trials in breast cancer, metastatic CRPC, and other solid tumors, for a total of 5544 patients.[40] Onset of moderate/severe pain was 4.7 months with ZA and increased to 6.5 months with denosumab (HR = 0.83; 95%CI 0.76-0.92; p < 0.001). Strong opioid use and worsening of health related quality-of-life were less common with denosumab.

Timing of administration of bone protecting agents

EAU and NCCN treatment guidelines recommend that bone metastatic CRPC patients should receive ZA or denosumab and recognize the superiority of the latter in delaying SRE.[19,21] None of the guidelines however provides practical recommendation on when to start, when to stop, and the interest of switching between agents. A supplementary analysis of the ZA registration trial indicated that ZA was more efficacious when initiated before the onset of pain.[41]

Noteworthy, EMA and FDA have granted regulatory approvals for ZA and denosumab in patients with hormone naïve prostate cancer with bone metastases, although published studies have been conducted only in CRPC patients. Since metastatic prostate cancer is unique in that it is so frequently responsive to first-line disease-modifying therapy, we believe that ZA and denosumab prescription should be restricted to CRPC patients.

Toxicity of bone targeted agents in metastatic CRPC

The most common expected toxicities are summarized in Table 4. In contrast to ZA, there is no need for denosumab dose-adjustment in case of renal impairment, a common problem in prostate cancer patients. In the denosumab registration trial, a dose adjustment for creatinine clearance at baseline and a dose withhold for serum creatinine increases occurred in 22% and 15% of patients receiving ZA, respectively.[31]

Hypocalcemia is a known adverse effect of anti-remodeling agents, which is more frequent in CRCP than other cancer type and with denosumab than with ZA (all grades: 12.8% denosumab versus 5.8%

TABLE 4. **Safety results of interest in a pooled analysis of the denosumab registration program. Adapted from Lipton et al[52]**

Patient incidence, n (%)	Zoledronic acid n (%)	Denosumab n (%)
Total patients	2386	2841
Infectious AEs	1218 (42.9)	1233 (43.4)
Infectious serious AEs	309 (10.9)	329 (11.6)
Acute phase reactions (first 3 days)	572 (20.2)	246 (8.7)
Cumulative rate of ONJ	37 (1.3)	52 (1.8)
Year 1	15 (0.5)	22 (0.8)
Year 2	28 (1.0)	51 (1.8)
Hypocalcemia	141 (5.0)	273 (9.6)
New primary malignancy	18 (0.6)	28 (1.0)
AEs leading to study discontinuation	280 (9.9)	270 (9.5)

AEs = adverse effects; ONJ = osteonecrosis of the jaw

ZA).[31,42] Grade 3 hypocalcemia (corrected serum calcium (CSC) < 7.0 mg/dL-6.0 mg/dL; ionized calcium < 0.9 mmol/L-0.8 mmol/L; hospitalization indicated) or 4 (CSC < 6.0 mg/dL; ionized calcium < 0.8 mmol/L; life-threatening consequences) has been reported in 5.1% of patients with denosumab and 1.4% with ZA. The risk of developing hypocalcemia is mainly increased among patients with impaired renal function (creatinine clearance < 30 mL/min).[43] This is likely due to reduced renal calcium reabsorption, insufficient conversion of vitamin D to its active metabolite and impaired phosphorus excretion. Pre-existing hypocalcemia must be corrected before starting denosumab or ZA. Initial monitoring of calcium levels is recommended. All patients but those with hypercalcaemia should be given calcium (≥ 500 mg/d) and vitamin D oral supplements (≥ 400 IU/d) and should have their serum calcium concentration checked on a monthly basis for instance. Should hypocalcemia occur, denosumab should be held until correction of hypocalcemia has been achieved.[44]

Osteonecrosis of the jaw (ONJ) was observed in 1%-2% of the study cohort (12 cases with zoledronic acid, 22 cases with denosumab; p = 0.09). Although ONJ may also occur spontaneously, local invasive dental procedures and concomitant oral disease have been identified as the most important local risk factors.[45] The cornerstone of ONJ prevention is thus traditionally to improve dental care and avoidance of invasive dental procedures once therapy has been started.[46,47] We must agree however that such recommendations are based on position papers and case reports, while evidence-based treatment recommendations are lacking.

The "Holy Grail" of metastases prevention

Non-metastatic (M0) CRPC patients are usually strictly asymptomatic and it has become a major challenge to cherish this asymptomatic health state as long as possible by extending bone metastasis free survival (BMFS).[27] This has consequently been the subject of several clinical trials, most of them being negative or inconclusive, Table 5. The tested agents include bisphosphonates clodronate and ZA, endothelin receptor type A inhibitors atrasentan and zibotentan, and denosumab. One of the reasons for failure is clearly the heterogeneity of that patient group and the usual very prolonged BMFS. In the first trial evaluating the benefit of ZA in M0 CRPC, median BMFS was 30 months and at 2 years, only 33% of the patients had developed bone metastases.[48]

Smith et al have recently reported the results on denosumab in a placebo-controlled trial in M0 CRPC patients with PSA ≥ 8 ng/mL and/or a PSA doubling time (DT) ≤ 10 months.[49] Denosumab significantly prolonged BMFS by a median of 4.2 months compared with placebo, but the benefit/side effects ratio was deemed insufficient to grant registration in that setting. There was indeed a significant risk of osteonecrosis of the jaw (5% in the denosumab arm versus 0% in the placebo arm) and hypocalcemia (2% in the denosumab arm versus < 1% in the placebo arm).

Prevention of bone metastasis is therefore still a major issue to be tackled.

TABLE 5. **Summary of bone metastasis prevention trial in non-metastatic prostate cancer patients treated with androgen deprivation therapy**

Study	Patients	Treatment arms	Endpoints	
MRC PR04[53]	T_{2-4}	Clodronate versus placebo	Time to symptomatic BM or prostate cancer death, OS	Primary not met
Zometa 203[48]	M0 CRPC	ZA versus placebo	Time to first BM, OS, BMFS	Terminated early
RADAR	T2a (Gleason ≥ 7, PSA ≥ 10 ng/mL); or T_{2b-4}, N_0	EBRT + ADT ± ADT	PSA, PFS, OS, BMFS	Ongoing
STAMPEDE	High risk patients starting ADT	ADT + placebo or ZA or docetaxel or combination	OS, QoL, SREs, PFS	Ongoing
ZEUS	Gleason 8-10; pN_+ or PSA ≥ 20 ng/mL	ZA versus standard treatment	BM rate, OS, PSA DT	Primary not met
M00-244[54]	M0 CRPC	Atrasentan versus placebo	BMFS, PSA, PFS, OS	Primary not met
Enthuse M0[55]	M0 CRPC	Zibotentan versus placebo	BMFS, OS	Terminated early
Study 147[49]	M0 CRPC	Denosumab versus placebo	BMFS, OS	BMFS + 4.2 months for denosumab

BM = bone metastasis; BMFS = bone metastasis free survival; EBRT = external beam radiotherapy; PFS = progression free survival; ZA = zoledronic acid; , DT = doubling time; OS = overall survival; QoL = quality-of-life; SRE = skeletal related event
STAMPEDE includes M0 and M+ patients

Conclusions

Preserving skeletal integrity is a key component of the management of advanced prostate cancer. Indeed, the skeleton is the primary dissemination site for metastatic cells and ADT, the reference systemic treatment, profoundly affects bone physiology.

The bone mineral density of patients receiving ADT should be periodically checked by DXA scan, especially if they carry additional risk factors for osteoporosis. Lifestyle adjustments, including weight-bearing exercises, and appropriate calcium-vitamin D intake should be recommended to every ADT patient. Bisphosphonates or denosumab should be discussed in case of osteoporosis.

In CRPC patients, bone is the most frequent metastatic site. Bone metastases can grow rapidly and cause debilitating complications. Bisphosphonates or denosumab effectively delay these complications and should be part of the standard armamentarium in progressing metastatic CRPC patients. A careful monitoring of patients, with a special attention on calcium/vitamin D intake and oral hygiene, their safety, is required to secure an acceptable toxicity profile.

Based on the current evidence, there is no indication of bisphosphonates or denosumab in bone metastatic hormone naïve or hormone responsive patients, or in non-metastatic CRPC to prevent the onset of bone metastases.

Disclosure

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