Canadian Urological Association best practice report: Bone health in prostate cancer

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Introduction

Men diagnosed with prostate cancer are living longer due to advances in treatment. As a result, increased attention to cancer treatment-induced bone loss, as well as optimizing care of men with castrate-resistant prostate cancer (CRPC) and bony metastases are needed. Androgen deprivation therapy (ADT) with gonadotropin-releasing hormone agonists, antagonists, or orchiectomy decreases bone mineral density (BMD) and increases the risk of fracture.[1] Men with prostate cancer often have other risk factors for low BMD, including advanced age, smoking, low protein intake, family history of osteoporosis, glucocorticoid use, and a prior history of fall or fracture.[2,3] Fractures cause significant morbidity. One-third of Canadian men who experience a hip fracture die within one year, and hip fracture is an independent risk factor for mortality.[4,5] Previous reports indicate that men on ADT have low rates of osteoporosis screening and infrequently receive interventions to reduce bone loss.[6,7] The cumulative impact of systemic prostate cancer treatments on bone health has become an important aspect of patient-centered, comprehensive prostate cancer care.

Objective

The objective of this best practice report is to provide recommendations to help optimize bone health in Canadian patients with prostate cancer receiving ADT. These recommendations are applicable to all physicians who initiate men on ADT, including urologists, radiation and medical oncologists, and family physicians. This report will focus on the assessment and management of cancer treatment-induced bone loss. Guidelines regarding the management of prostate cancer bone metastases are covered in other Canadian Urological Association (CUA) guidelines.[8,9]

Methodology

A working group was assembled that included urologists, a radiation oncologist, and an endocrinologist with expertise in osteoporosis. A review of the literature was performed for relevant articles from PubMed, Medline, and the Cochrane Library database. Existing guidelines related to prostate cancer and osteoporosis were also reviewed. Bibliographies of relevant articles were reviewed to identify additional articles. Recommendations were generated by consensus.

Bone physiology and cancer treatment-induced bone loss

Bone remodelling is a continuous physiological process whose function is to maintain bone integrity. Osteoclasts induce bone breakdown (resorption), and osteoblasts perform bone synthesis (ossification). Osteoblasts express the androgen receptor. The presence of androgens results in improved

bone density in at least two ways. First, androgens stimulate osteoblast proliferation. Second, androgens are peripherally converted to estrogens, and estrogens downregulate osteoclast activity via the receptor activator of nuclear factor kappa-B (RANK).[10] When the RANK ligand (RANKL) binds to RANK, osteoclast differentiation, activation, and survival are increased. Estrogens inhibit the RANKL/RANK pathway, reducing osteoclast activity, and decreasing bone resorption.[11] Therefore, when androgen levels are decreased, bone density is reduced through downregulation of osteoblasts and upregulation of osteoclasts.[12,13]

ADT reduces testosterone, which disrupts bone homeostasis and promotes net bone resorption, thereby reducing BMD. In men on ADT, BMD decreases at an accelerated rate compared to healthy controls, with the most significant changes occurring in the first year of therapy.[14] Loss of BMD is progressive over time, with up to 85% of men having osteoporosis after 10 years of ADT, and up to 20% experiencing a fracture within the first five years.[15,16] Other cancer therapies, frequently used in conjunction with ADT, may also have adverse effects on bone integrity. Glucocorticoids increase bone loss by inducing osteoblast apoptosis and increasing osteoclast survival.[17] Androgen receptor axis-targeted (ARAT) therapies, such as abiraterone, enzalutamide, apalutamide, and darolutamide, may also be associated with an increased risk of osteoporotic fracture.[8,9,18] A recent systematic review of randomized trials reported the use of ARATs was associated with a 1.6-fold increased risk of fracture and a 1.8-fold increased risk of falls compared to similar men not receiving ARATs.[19] A similar increase in fracture risk was observed in patients receiving abiraterone acetate compared to placebo (5.9% vs. 2.3%).[20]

In summary, with treatment advances leading to longer periods of survival for men with advanced prostate cancer, many patients have prolonged exposure to medications that accelerate bone loss. Physicians who manage men with prostate cancer on ADT should include assessment of bone health in their routine care to try to prevent treatment-induced bone loss.

Recommendations

Assessment

Recommendation 1: Men on ADT should be evaluated for fracture risk. Fracture risk can be estimated using the FRAX or CAROC risk assessment tools and/or BMD assessment with a dual energy X-ray absorptiometry (DXA) scan.

Men initiating ADT of any duration should have an assessment of their individual fracture risk. The minimum duration of ADT exposure that induces clinically significant BMD

loss is unknown and may vary by patient. Furthermore, some men will have low BMD prior to initiating ADT. For these reasons, all men initiating ADT should be evaluated for fracture risk, especially those initiating ADT for one year or greater.

The World Health Organization fracture risk assessment (FRAX) algorithm provides an estimate of an individual's 10-year fracture risk and has been validated for the Canadian population (*www.sheffield.ac.uk/FRAX/tool.aspx?country=19*).[21] FRAX incorporates a patient's femoral neck T-score from a DXA scan with other risk factors for fracture, including age, body mass index (BMI), glucocorticoid use, prior fracture history, rheumatoid arthritis, smoking, alcohol consumption, and parental hip fracture history (Table 1).[22] FRAX can also estimate fracture risk without a DXA scan. When using FRAX, ADT can be included in the score as a secondary cause of osteoporosis. The Canadian Association of Radiologists and Osteoporosis Canada (CAROC) tool is another validated assessment score that requires only five clinical parameters to estimate an individual's risk of fracture: age, sex, fragility fracture history, glucocorticoid use, and femoral neck T-score from a DXA scan (*www.osteoporosis.ca*).[23]

BMD measured by DXA is one component of fracture risk assessment. BMD measurements are taken at the lumbar spine and hip and reported as T-scores, which describe the number of standard deviations below or above the mean value for a healthy 30-year-old of similar sex. Osteoporosis is defined as a T-score value 2.5 standard deviations or more

Table 1. Risk factors for osteoporotic related fracture[23]	
Risk factor	**Description**
Previous fracture (fragility)	Spontaneous fractures or those induced by a minimal trauma that would not normally be expected to cause a fracture. Also includes asymptomatic vertebral fractures.
Glucocorticoid use	Oral glucocorticoids equivalent to ≥5 mg/day of prednisone (FRAX) or ≥7.5 mg of prednisone (CAROC) for >3 months.
Parental history of hip fracture	Mother or father with a history of hip fracture at age <80 years.[61]
Age	Older age is associated with higher risk. FRAX includes ages 40–90 years, while CAROC includes ages 50–85.
Height and weight (BMI)	Low BMI is associated with higher risk of fracture.
Tobacco use (smoking)	Men who are currently smoking.
Alcohol consumption	Consumption of ≥3 alcoholic beverages per day.
Rheumatoid arthritis	Rheumatoid arthritis is a risk factor. Osteoarthritis is not a risk factor.

BMI: body mass index; CAROC; The Canadian Association of Radiologists and Osteoporosis Canada fracture risk assessment; FRAX: The World Health Organization fracture risk assessment algorithm.

below the mean (T≤ - 2.5), and osteopenia is defined as a T-score between 1 and 2.5 standard deviations below the mean (T -1 to -2.5). It is important to note that BMD scores alone may underestimate fracture risk, as many men with fractures have BMD scores that are not in the osteoporotic range.[24] It is thus recommended to incorporate BMD scores and other patient risk factors in a validated calculator to obtain the best assessment of fracture risk.

Recommendation 2: Treatment to prevent bone loss should be initiated in patients on ADT with: osteoporosis (T-score ≤ -2.5), or a prior fragility fracture, or a 10-year major osteoporotic fracture risk of > 20%.

Recommendations for initiating treatment with a bone targeted therapy include osteoporosis (any T-score ≤ -2.5), or a prior fragility fracture, or a 10-year probability of major osteoporotic fracture >20%.[25,26] A fragility fracture is a fracture after minimal mechanical force (e.g., fall from standing height) that would not ordinarily be expected to cause a

fracture. A fragility fracture is a predictor of future fracture, independent of FRAX or CAROC score. Men on ADT with a moderate risk of fracture on FRAX or CAROC (10-year major osteoporotic fracture risk between 10% and 20%) may benefit from treatment, and a shared decision-making process to explore the patients' values and preferences is suggested.[25] Osteoporosis Canada recommends ongoing BMD surveillance every 1–3 years.[25] Men on ADT at low risk of fracture may be followed every 2–3 years with a repeat BMD. Men on ADT at moderate or high risk of fracture who are not receiving pharmacological treatment for bone loss should have a repeat BMD every 1–2 years. For men receiving pharmacological treatment, a repeat BMD within the first two years is a reasonable approach to assess for treatment efficacy. Fig. 1 summarizes the assessment of fracture risk and treatment.

For men on ADT who initiate a bisphosphonate to prevent bone loss, it is reasonable to stop the bisphosphonate after a period of treatment if repeat risk assessment with FRAX or CAROC indicates they are no longer at elevated risk of
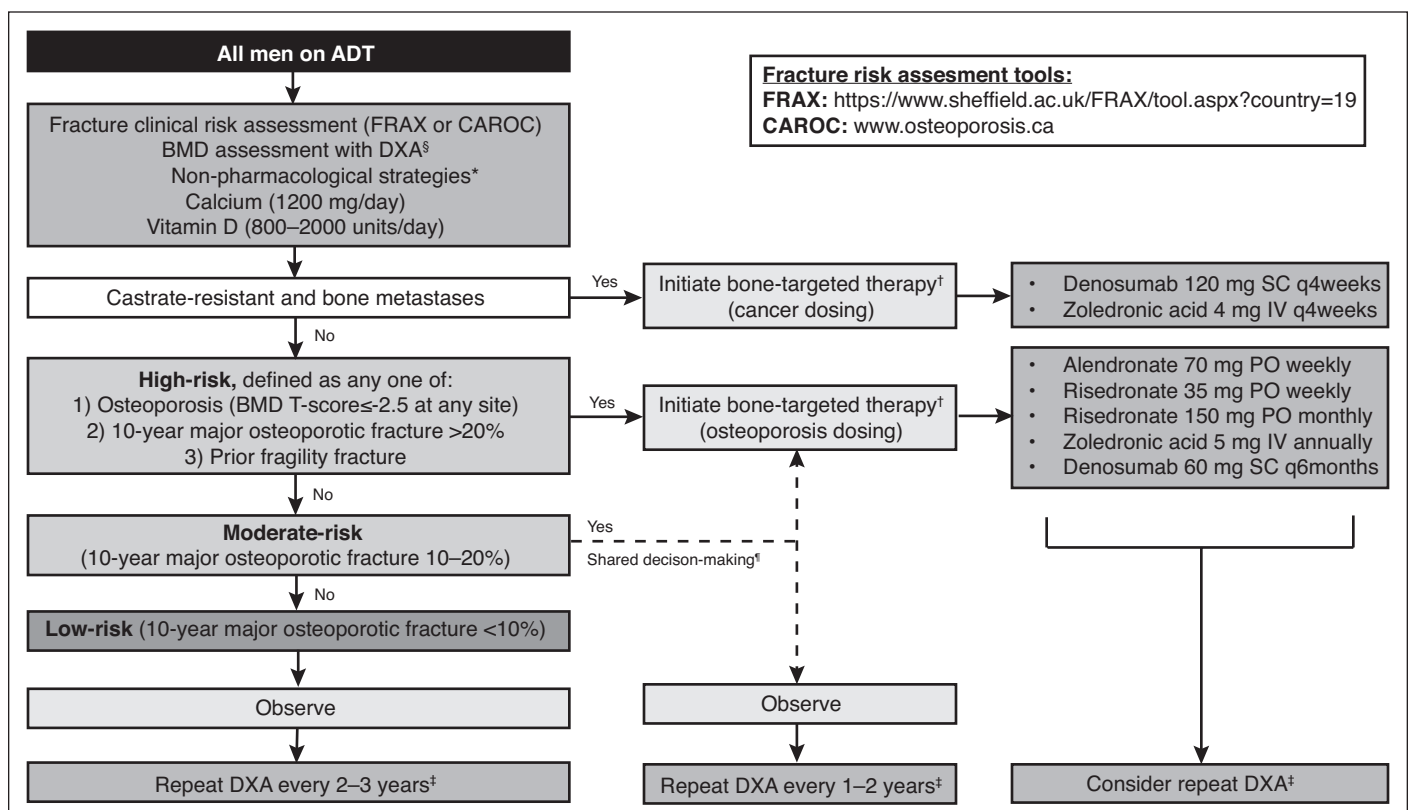
Fig. 1. Assessment and management of bone health in men on ADT. §Baseline DXA is useful to assess fracture risk. If DXA cannot be performed, fracture risk can be assessed using FRAX or CAROC without DXA. *Non-pharmacological strategies include smoking cessation, moderation of alcohol consumption, exercise, and fall prevention. ¶The Canadian Osteoporosis Society recommends bone targeted agents may be considered in men on ADT with moderate risk of 10-year major osteoporotic fracture (10–20% risk). A shared decision-making approach is appropriate. May consider referral to an osteoporosis expert for patients wishing to discuss further. ‡Evidence to guide the optimal interval to repeat a DXA scan and BMD assessment is limited. The panel recommends clinicians consider repeat DXA every 2–3 years in low-risk patients and every 1–2 years for moderate-risk patients who are not on treatment or when new clinical factors/treatments arise that may impact bone health. Men on bone-targeted therapy may consider a repeat DXA scan to confirm effectiveness of therapy. †Recommend baseline serum calcium and creatinine. ADT: androgen deprivation therapy; BMD: bone mineral density; CAROC: The Canadian Association of Radiologists and Osteoporosis Canada fracture risk assessment; DXA: dual energy X-ray absorptiometry; FRAX: The World Health Organization fracture risk assessment algorithm.

fracture. This may be especially relevant for patients after a fixed course of ADT, for example when ADT is given with radiation for localized prostate cancer. Furthermore, while the benefits of bone-targeted therapy generally outweigh the risks even after 10 continuous years of bisphosphonate therapy, there have been concerns of atypical femoral fracture associated with prolonged use, prompting consideration of a drug holiday for patients receiving long-term bisphosphonates to prevent bone loss.[27] Men may consider a one-year bisphosphonate holiday after three years of intravenous or five years of oral bisphosphonate therapy, provided they don't have a history of fragility hip or vertebral fracture, have no more than one fragility fracture, hip BMD T-scores> -2.5, and are not high risk for fracture as per FRAX. Denosumab should generally not be discontinued abruptly, as this may lead to rapid bone loss and a risk of rebound fracture. Discontinuation of denosumab should, therefore, be done in conjunction with an osteoporosis expert.

Education

Recommendation 3: Patients initiating ADT should receive education regarding cancer treatment-induced bone loss, its consequences, and prevention strategies.

Education empowers patients, increases autonomy, and improves health outcomes.[28] Many patients with prostate cancer have limited knowledge of how cancer treatments may induce bone loss.[29] Educational interventions provided through information pamphlets, family physicians, and bone health coordinators have been shown to improve the uptake of BMD testing and pharmacotherapy for men on ADT.[6] Online educational materials have been shown to improve bone health knowledge in prostate cancer survivors and are an easy method to disseminate information.[30]

Lifestyle modification

Recommendation 4: Patients initiating ADT should be educated on smoking cessation, moderation of alcohol consumption, weight-bearing and balance exercises, and fall prevention strategies where appropriate.

Lifestyle modifications can reduce bone loss and fracture risk for men with prostate cancer on ADT. Smoking cessation, reducing alcohol consumption to less than three alcoholic beverages per day, increasing exercise, and interventions to reduce the risk of falls are suggested.[25,31,32] A systematic review focusing on prostate cancer patients suggested exercise may help preserve lumbar spine, hip, and femoral shaft BMD.[32] Maximum effects may be seen with moderate-intensity weight-bearing aerobic, resistance, and impact exercises. However, none of the studies included

in the systematic review assessed exercise as a means of directly reducing the risk of falls or fractures. Regardless, physical exercise has numerous known health benefits and can improve quality of life measures in prostate cancer patients.[32,33] Recommendations for reducing falls and fractures include balance exercises, posture awareness, and spine-sparing strategies, such as sitting while tying shoes or bending at the knees when lifting.[25] Ongoing studies are required to further quantify the benefit of these interventions.

Calcium and vitamin D

Recommendation 5: Patients on ADT should target calcium intake of 1200 mg/day and consider calcium supplementation if dietary calcium is inadequate. Patients on ADT should target 800–2000 IU of vitamin D daily.

Calcium and vitamin D supplementation may prevent bone loss and reduce fractures.[34] Calcium is deposited into bone tissue through ossification by osteoblasts. Vitamin D is synthesized in the skin upon exposure to ultraviolet light and increases intestinal absorption of calcium. A meta-analysis of randomized controlled trials in adult patients without cancer found that daily supplementation of vitamin D and calcium reduces hip fracture by 6% and any fracture by 16%.[35] No reduction in fracture was observed with vitamin D supplementation alone. In patients with prostate cancer on ADT, calcium and vitamin D supplementation are independent predictors of higher BMD scores during the first year of treatment.[36] The recommended calcium intake is 1200 mg per day from all sources and vitamin D supplementation is 800–2000 IU.[9,25] Supplementation up to 2000 IU per day of vitamin D can be done safely without monitoring.[25] Intake of lower doses of calcium or vitamin D than the provided targets are inadequate to prevent treatment-induced bone loss.[37]

Bone-targeted therapies

Bone targeted therapies are pharmacotherapies that actively prevent bone loss by preventing bone resorption. Two main drug classifications are relevant for patients with cancer treatment-induced bone loss. Bisphosphonates are analogues of pyrophosphate that concentrate in the bone and inhibit osteoclast function by reducing osteoclast recruitment to the bone surface. This reduces osteoclast activity and promotes osteoclast apoptosis.[34] Denosumab is a monoclonal human antibody that binds the RANKL. This prevents the RANKL from activating the RANK receptor on osteoclasts. This reduces osteoclast formation, activity, and survival.

There are two patient populations in which to consider bone-targeted therapies: 1) any patient on ADT at elevated risk of osteoporotic fracture (see Recommendation 2); and 2) any man with CRPC and bone metastases regardless of

other fracture risks. The first indication applies to all men exposed to ADT regardless of prostate cancer disease state. Patients with CRPC and bone metastases are currently the only disease state with recommendations for routine bone-targeted therapies. Of note, recommended dosing of bone targeted therapies differs based on the indication (Fig. 1). The evidence for bone-targeted therapies in the various prostate cancer disease states are discussed below. Finally, while many physicians who manage prostate cancer will be able to initiate therapy to prevent bone loss, referral to a medical specialist with expertise in osteoporosis should be considered if there are: intolerance or contraindications to bone-targeted therapy, fractures, BMD that does not improve or worsens on therapy, or for patients with multiple risk factors, unclear clinical risk factors, or desiring more detailed risk-benefit discussions.

Management of specific patient populations

Recommendation 6: Men with castrate-sensitive prostate cancer (CSPC) and non-metastatic CRPC should not receive bone-targeted therapies for the prevention of skeletal-related events (SREs). Treatment for the prevention of bone loss should be considered in all men on ADT as per Recommendation 2.

Non-metastatic CSPC

A randomized trial of men on ADT receiving zoledronic acid 4 mg intravenous (IV) every three months for one year or placebo reported an increase in BMD by 5.6% in the zoledronic acid group compared to a decrease in BMD of 2.2% in the placebo group at one year (p<0.001).[38] A systematic review of bisphosphate use in men with prostate cancer showed improvements in BMD but not in fracture risk.[39] A randomized trial of patients on ADT receiving denosumab 60 mg subcutaneous (SC) every six months or placebo reported that denosumab significantly increased BMD by 5.6% compared to a 1% decrease in the placebo group at two years (p<0.001). Denosumab also significantly reduced vertebral fracture risk from 3.6% to 1.5% in men on ADT without metastases at 36 months (p=0.006) with a number needed to treat (NNT) of 48.[40] A single study compared denosumab to the oral bisphosphonate alendronate and found significant improvement in lumbar BMD at 24 months with denosumab (5.6% vs. -1.1%), with a non-statistically significant decrease in vertebral fracture risk.[41]

In summary, while bone-targeted therapies may impact BMD, they have not been shown to reduce SREs in men with non-metastatic CSPC. SREs are defined as pathological fracture, spinal cord compression from cancer, or the need for radiation or surgery to manage pain or reduce future fracture risk.[42] Therefore, at this time in non-metastatic CSPC, bone-targeted therapies are only indicated in men who are at increased risk of osteoporotic fracture.

Metastatic CSPC

The routine use of bone-targeted therapies has not been shown to prevent skeletal metastasis or reduce SREs in men with metastatic CSPC.[43] The CALGB 90202 study determined that early treatment with zoledronic acid in metastatic CSPC was no different than placebo in preventing fractures or improving survival.[44] Similarly, zoledronic acid with and without docetaxel showed no improvement in SREs in the STAMPEDE trial.[45] Finally, the ZAPCA trial found no difference in time to treatment failure or first SRE when comparing zoledronic acid to placebo.[46] Therefore, at this time in metastatic CSPC, bone-targeted therapies are only indicated in men who are at increased risk of osteoporotic fracture.

Non-metastatic CRPC

There are few studies assessing the role of bone-targeted therapies in non-metastatic CRPC. In one study, denosumab 120 mg SC every four weeks delayed the time to first bone metastasis in patients with non-metastatic CRPC and a prostate-specific antigen (PSA) doubling time of <10 months, however, did not result in an improvement in progression-free or overall survival (NNT= 20).[47] A randomized trial of zoledronic acid for the prevention of first bone metastasis was terminated due to the low observed event rate.[48] Neither zoledronic acid nor denosumab has been approved in Canada for prevention of bony metastases in men with prostate cancer, due to uncertain clinical benefit with definite risk of complications.

Metastatic CRPC

Recommendation 7: Men with CRPC and bone metastases should receive denosumab 120 mg SC every four weeks (preferred) or zoledronic acid 4 mg IV every four weeks to prevent SREs.

Bone-targeted therapies are indicated in men with CRPC and bone metastases to reduce SREs.[8] Zoledronic acid given at 4 mg IV every four weeks has been shown to reduce SREs from 49% to 38% at 24 months compared to placebo (NNT=9).[49] A randomized controlled trial comparing denosumab to zoledronic acid, found denosumab was superior, as it prolonged the time to first SRE by 3.6 months (NNT=20).[50] Dose de-intensification has been studied to determine the efficacy of prolonging the interval between doses of bone-targeted therapies. Zoledronic acid given at 12-week intervals was found to be non-inferior to four-week dosing for the prevention of SREs in a mixed population of prostate, breast and multiple myeloma patients and may be an acceptable dosing alternative.[51] Denosumab given at 12-week compared to four-week intervals was non-inferior for health-related quality of life, but was underpowered for assessment of fractures.[52] An ongoing

trial is exploring the role of every 12-week denosumab in metastatic CRPC patients (NCT02051218).

Adverse events

Recommendation 8: Patients receiving bone-targeted therapies, including zoledronic acid and denosumab, should be counselled regarding osteonecrosis of the jaw and should receive a baseline dental exam prior to initiating therapy. Baseline renal function and serum calcium should be assessed.

Osteonecrosis of the jaw (ONJ) is a potential complication of bone-targeted therapies. It is very rare to experience ONJ using osteoporotic treatment doses of bone-targeted therapies. The risk of ONJ is higher in patients with CRPC and bony metastases who are receiving a bone-targeted therapy for prevention of SREs. Other risk factors for ONJ include prior head and neck radiotherapy, glucocorticoid exposure, diabetes, poor dental hygiene, or those undergoing invasive dental procedures.[25,53,54] A study assessing safety across multiple trials showed no significance difference in developing ONJ after one year of therapy on monthly denosumab or zoledronic acid when standardized for exposure time (1.1% vs. 0.7% per 100 years of exposure).[55] Longer-term follow-up of patients on denosumab found the incidence increased to 4.1% per 100 years of exposure, suggesting the risk of ONJ increases with time. It is recommended to perform a baseline dental exam and to resolve dental issues prior to starting a bone-targeted agent. For patients requiring invasive dental procedures while on a bone-targeted agent, there is no evidence that interrupting treatment will reduce ONJ risk.[56]

Zoledronic acid, unlike denosumab, requires dose adjustments for renal failure and it is recommended to cease therapy with a creatinine clearance (CrCl) <30 mL/min.[9,25] Routine monitoring is not usually required for patients receiving osteoporosis dosing regimens. Severe hypocalcemia occurs in <1 % of patients. Risk factors include osteoblastic metastasis, vitamin D deficiency, and renal insufficiency.[57] Periodic calcium monitoring can be considered in patients with metastatic CRPC receiving treatment to prevent SREs and in patients with borderline renal function.[55]

Special situations

Patients receiving second-generation antiandrogens and radium-223

Recommendation 9: Combining radium-223 and ARAT therapies should be avoided due to increased fracture risk until further data is available.

Radium-223 is an alpha-emitting radiopharmaceutical that has been shown to improve overall survival in men with CRPC and symptomatic bony metastases.[58] The combination

of radium-223 in addition to abiraterone has recently been shown to increase fracture risk and should be avoided. The ERA 223 study was a randomized controlled trial of abiraterone with and without radium-223.[59] The combination of radium-223 and abiraterone had higher rates of overall fracture (29% vs. 11%) and non-pathological fracture (49% vs. 17%) compared to abiraterone alone. The overall use of additional supportive bone-targeted therapies in the study population was low, at 40% and a post-hoc analysis determined the use of bone-targeted therapies decreased the risk of fracture. PEACE III (NCT02194842) is an ongoing study assessing the combination of radium-223 and enzalutamide with protocol changes to include routine bone-targeted therapies. An interim analysis of PEACE III showed a three-fold higher risk of fracture with combination treatment that was reversed with mandatory bone-targeted therapy administration.[60] These results stress the ongoing importance of bone health assessment and bone-targeted therapies in men with CRPC and bony metastases.

Conclusions

This best practice report aimed to provide physicians with recommendations to help optimize bone health in patients with prostate cancer receiving ADT. Prostate cancer treatments affect bone health and men starting ADT should be assessed for fracture risk. Multiple strategies exist to improve bone health, including lifestyle modifications, calcium and vitamin D supplementation, and bone-targeted therapies for at-risk patients. Ongoing research assessing the impact of comprehensive bone health strategies to reduce cancer treatment-induced bone loss in prostate cancer patients is needed.

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