Bone Health in Patients with Prostate Cancer

Effective Date: January, 2022
Background

Androgen deprivation therapy (ADT) is the main therapeutic approach for men with advanced or metastatic prostate cancer. Despite the potential benefits associated with its use, ADT can cause a range of side effects that negatively affect quality of life including osteoporosis and bone fracture. ADT therapy for prostate cancer increases bone turnover, decreases bone mineral density, and increases the risk of bone fractures.¹ Loss of bone mineral density can be detected after as little as 6 months of ADT.² Men who are receiving ADT experience bone loss at approximately 9-fold the rate of a healthy male.³ Among men with non-metastatic prostate cancer the risk of developing osteoporosis is influence by the duration of ADT. Osteoporosis occurs in approximately 36, 43, 49, 60, 66, and 81% of patients after 0, 2, 4, 6, 8, and 10 years of ADT, respectively,⁴ and up to 20% of men will experience osteoporotic skeletal fracture within 5 years of starting ADT.⁵, ⁶

Guideline Questions

How should bone health be monitored in patients receiving therapy for non-metastatic, metastatic castrate sensitive, or metastatic castrate resistant prostate cancer?

Search Strategy

An informal non-systematic literature search of relating guidelines from other jurisdictions and primary literature was performed.

Target Population

Adult males (≥18 years) who have been diagnosed with prostate cancer.

Recommendations

General Recommendations

1. All patients with prostate cancer should ensure adequate calcium and vitamin D intake, using supplements if necessary.⁷

2. For patients being treated for prostate cancer, an assessment of risk for osteoporosis should be performed. The Fracture Risk Assessment Tool (FRAX®) is recommended for calculating the ten year probability of fracture with BMD.
   - Low risk for osteoporosis - no high-risk characteristics.
   - High risk for osteoporosis - any of the following:
     - ADT > 6 months
     - Previous fracture
     - Family history of osteoporosis
     - Low body weight
     - Smoker
     - Excessive alcohol intake
- Steroid use
- Low vitamin D levels

Management Options for Patients with Non-Metastatic Disease

1. Calcium 1200-1500mg and Vitamin D 800-2000 IU daily is recommended for all men on ADT.\textsuperscript{8, 9}

2. Baseline dual energy X-ray absorptiometry (DEXA) scan for all patients.

3. If DEXA reveals osteoporosis (T-score <-2.5) then bisphosphonate therapy should be initiated as per standard treatment protocols. Treatment of osteoporosis with bisphosphonates should be undertaken with oral agents that have been approved by Health Canada.\textsuperscript{10-12}

4. If DEXA reveals osteopenia (T-score -1 to -2.5) or normal findings, then close follow-up is recommended as suggested below. Initiate treatment with bisphosphonates only if osteoporosis is diagnosed.

5. Concurrent bisphosphonate treatment at the initiation of ADT to prevent bone loss and the development of osteoporosis cannot be recommended at this time. Studies of immediate bisphosphonate use concurrent with ADT have been undertaken and in small sample sizes have been shown to increase bone mineral density (BMD). However, this has not been translated into a change in fracture risk, hence, the lack of recommendation to routinely use bisphosphonates prophylactically.

6. The diagnosis and treatment of osteoporosis may be undertaken by the person most familiar with the treatment of this condition. This may be the family physician but the individual who prescribes ADT (urologist, medical oncologist, radiation oncologist) should raise the issue and notify the family physician, through the consult note, of the recommendations regarding the management of bone health.

Management Options for Patients with Castrate-Sensitive Metastatic Disease

1. Calcium 1200-1500mg and Vitamin D 800-2000 IU daily is recommended for all men on ADT.\textsuperscript{8, 9}

2. All men being placed on ADT for metastatic prostate cancer should have a baseline assessment of osteoporosis risk and have a DEXA scan. Even after discontinuation of ADT, these patients are at risk of osteoporosis and a higher risk of vertebral and hip fractures.\textsuperscript{13}

3. If DEXA reveals osteoporosis (T-score <-2.5) then bisphosphonate therapy should be initiated as per standard treatment protocols. Treatment of osteoporosis with bisphosphonates should be undertaken with oral agents that have been approved by Health Canada. \textsuperscript{10-12}
4. If DEXA reveals osteopenia (T-score -1 to -2.5) or normal findings, then close follow-up is recommended as suggested below. Initiate treatment with bisphosphonates only if osteoporosis is diagnosed.

5. The diagnosis and treatment of osteoporosis may be undertaken by the person most familiar with the treatment of this condition. This may be the family physician but the individual who prescribes ADT (urologist, medical oncologist, radiation oncologist) should raise the issue and notify the family physician, through the consult note, of the recommendations regarding the management of bone health.

6. The routine use of any prophylactic bone targeted therapy (in the absence of DEXA scan proven osteoporosis) for the prevention/delays of osteoporotic skeletal complications cannot be recommended at this time.

7. The use of a bone targeted therapy in this clinical setting cannot be claimed to alter skeletal related events (SREs) or survival. Should men develop castrate resistant disease, then consideration should be given to more specific bone targeted therapies (see “Management Options for Patients with Castrate-Resistant Metastatic Disease” below).

Management Options for Patients with Castrate-Resistant Metastatic Disease

1. Calcium 1200-1500mg and Vitamin D 800-2000 IU daily is recommended for all men on ADT. 8, 9

2. Bone Health is important both to manage/monitor for osteoporosis and for the prevention or delay in skeletal related events.

3. Monitor osteoporosis with DEXA scans, follow osteoporosis guidelines. (CMAJ 2010 guideline: [Link](#))

4. Prior to initiation of therapy, a general oral exam should be performed and referral to dentistry if there are any concerns.

5. For the prevention of SREs, consider zoledronic acid or denosumab, although neither option is currently funded in Alberta.
   - **Zoledronic Acid (4mg IV q4weekly or q12 weekly).** Zoledronic acid has been shown to be superior to placebo in reducing bone pain and SREs. 14, 15 An interim analysis of the phase III CALGB 70604 trial involving 1822 patients (n=660 prostate) did not show a significant difference in SREs between prostate cancer patients who received zoledronic acid q4 vs q12 weekly. 16
   
   - **Denosumab (120mg SC q4weekly or q12weekly).** A phase III trial of 1904 patients with castration-resistant prostate cancer with no previous exposure to intravenous
bisphosphonate randomly assigned patients to denosumab or zoledronic acid. With a median duration on study of 12.2 months, median time to first on-study SRE was 20.7 months on denosumab compared with 17.1 months on zoledronic acid (HR 0.82; 95% CI 0.71-0.95; p<0.001 for non-inferiority; p=0.008 for superiority); adverse events were comparable.\textsuperscript{17} The ReaCT-BTA trial evaluated q12week vs q4week dosing intervals for denosumab, pamidronate, or zoledronic acid and preliminary results show that q12weekly dosing is not inferior to q4weekly dosing.\textsuperscript{18} Denosumab is not publicly funded in Alberta.

- **Duration of Therapy:** Optimal duration of therapy is not well defined but should be re-evaluated after 2 years.

6. The diagnosis and treatment of osteoporosis may be undertaken by the person most familiar with the treatment of this condition. This may be the family physician but the individual who prescribes ADT (urologist, medical oncologist, radiation oncologist) should raise the issue and notify the family physician, through the consult note, of the recommendations regarding the management of bone health.
References


18. Clemons Mj OMSCEDSBCMCMMRAGBPSJA. A randomized trial comparing four-weekly versus 12-weekly administration of bone-targeted agents (denosumab, zoledronate, or pamidronate) in patients with bone metastases from either breast or castration-resistant prostate cancer. J Clin Oncol. 2019;37 suppl(abstract 11501)
Development and Revision History
This guideline was reviewed and endorsed by the Alberta Genitourinary (GU) Tumour Team. Members include urologists, radiation oncologists, medical oncologists, nurses, pathologists, and pharmacists. Evidence was selected and reviewed by a working group comprised of members from the Alberta GU Tumour Team and a knowledge management specialist from the Guideline Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Resource Unit Handbook.

This guideline was originally developed in 2022.

Maintenance
A formal review of the guideline will be conducted in 2023. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

Abbreviations
ADT, androgen deprivation therapy; BMD, bone mineral density; DEXA, dual energy X-ray absorptiometry; FRAX, Fracture Risk Assessment Tool; SRE, skeletal related event.

Disclaimer
The recommendations contained in this guideline are a consensus of the Alberta Provincial GU Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

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