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Bone Health and Bone-Targeted Therapies for Prostate Cancer

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Guideline 3-14 Version 2 is comprised of 5 sections. You can access the summary and full report here:
https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/31716

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Bone Health and Bone-Targeted Therapies for Prostate Cancer

Recommendations

This is a quick reference guide and provides the guideline recommendations only. For key evidence associated with each recommendation, the systematic review, and the guideline development process, see the Full Report.

GUIDELINE OBJECTIVE

To evaluate the effectiveness of therapies targeting bone across all stages of prostate cancer.

TARGET POPULATION

Men with prostate cancer.

INTENDED USERS

Healthcare professionals, health care administrators, medical or radiation oncologists who treat genitourinary cancer, urologists, radiologists, nuclear medicine physicians, geriatricians, primary care physicians, osteoporosis experts, patients, and media.

Table 1-1. Dosage definitions for denosumab and zoledronic acid.

Drug	Indication	Current recommended dosage
Denosumab	Osteoporosis	60 mg subcutaneous injection every six months
	Bone metastasis	120 mg subcutaneous injection every four weeks
Zoledronic acid	Osteoporosis	5 mg intravenous infusion once per year[a]
	Bone metastasis	4 mg intravenous infusion every three to four weeks[b]

[a]Dosage and frequency used in most of the published studies was a 4 mg intravenous infusion every 3 months. See qualifying statement for Question 1.
[b]Less frequent dosing (every 12 weeks) may be acceptable. See qualifying statement for Question 3.

RECOMMENDATIONS, KEY EVIDENCE, AND INTERPRETATION OF EVIDENCE

QUESTION 1

Can therapeutic interventions reduce osteoporosis-related outcomes in men with prostate cancer receiving androgen deprivation therapy (ADT)?

Recommendation:
1. For men with prostate cancer at high risk of fracture (with or without bone metastases) receiving ADT, denosumab at the osteoporosis-indicated dosage should be considered to reduce the risk of fracture. In situations or jurisdictions where denosumab is contraindicated or not available, a bisphosphonate is a reasonable option.

Qualifying statements:

- Fracture risk can be estimated based on risk prediction tools such as the World Health Organization Fracture Risk Assessment Tool (WHO FRAX) or the Canadian Association of Radiologists and Osteoporosis Canada (CAROC) tool [1,2].
- Baseline bone mineral density (BMD) testing with conventional dual X-ray absorptiometry is encouraged for men prior to starting ADT to help determine the risk of fracture and identify those individuals most likely to benefit from denosumab or bisphosphonates. If a BMD test has been performed in the past one to two years, a repeat BMD test is not likely to be informative prior to starting ADT unless the patient was initiated on denosumab or bisphosphonates.
- The optimum duration of therapy is unknown. Current studies provide results up to 36 months of therapy.
- The dosages used in the studies were:
    - Denosumab, 60 mg subcutaneous injection every six months [3] (See Table 1-1).
    - Alendronate, 70 mg oral dose each week [4,5].
    - Zoledronic acid (ZA), 4 mg intravenous (IV) infusion every three months [6-12], 4 mg IV every six months [13], and 4 mg IV once yearly [14]. Both Health Canada and the U.S. Food and Drug Administration have approved a 5 mg IV infusion dose for the treatment of osteoporosis in men, whereas neither agency has approved the 4 mg dose for the treatment of osteoporosis in men (See Table 1-1).
- Denosumab was shown to reduce fractures in this population. Other agents only improved BMD. However, there is substantial indirect evidence of fracture reduction in other populations with the use of bisphosphonates.
- Toremifene and raloxifene are selective estrogen receptor modulators (SERMs). Although both drugs were associated with increased BMD and toremifene reduced the risk of fracture, SERMs are associated with increased risk of venous thromboembolic events, raising safety concerns in this population.
- Three small trials comparing exercise programs with usual care [15-17] and one small trial comparing group exercise with personal training [18] showed no difference in BMD between groups. One trial showed improvements in quality of life measures with exercise [17]. A more comprehensive review of exercise for people with cancer is available (see Guideline 19-5: Exercise for People with Cancer).
- In patients with metastatic disease, fracture is part of the skeletal-related events (SRE) composite outcome (See question 3).
- Men with castration-sensitive prostate cancer with bone metastasis may derive benefit from starting or continuing denosumab at the osteoporosis-indicated dosage or a bisphosphonate for fracture prevention. However, few trials that were reviewed for this question included such men and analyses, stratified by the presence or absence of bone metastasis, were not performed. Therefore, the evidence of benefit is less compelling in this scenario.

QUESTION 2

Can therapeutic interventions prevent bone metastases in men with prostate cancer?

Recommendations:
2a. In men with high-risk localized prostate cancer, bisphosphonates are not recommended to reduce the risk of first bone metastasis. **2b. In men with nonmetastatic castration-resistant prostate cancer (CRPC), denosumab at the bone metastasis-indicated dosage is not recommended to reduce the risk of first bone metastasis.**
Qualifying statements:
• Denosumab has not been approved in Canada or the United States for this indication (2b). (www.fda.gov/downloads/Advisorycommittees/CommitteesMeetingMaterials/Drugs%20/OncologicDrugsAdvisoryCommittee/UCM293709.pdf) • Denosumab, 60 mg subcutaneously every six months, can still be used to prevent osteoporosis-related outcomes (see Recommendation 1).

QUESTION 3
Can bone-targeted therapies reduce the incidence of SREs, reduce pain, or improve quality of life in men with prostate cancer metastatic to bone?

Recommendation:
3a. In men with metastatic CRPC (mCRPC), either ZA (minimally symptomatic or asymptomatic disease) or denosumab (disease independent of symptoms) (both at bone metastasis-indicated dosages) is recommended for preventing or delaying SREs. Insufficient evidence exists to make a recommendation with respect to men with castration-sensitive prostate cancer and bone metastasis.

Recommendation:
3b. In men with symptomatic mCRPC and bone pain, radium (Ra)-223 should be considered for reducing symptomatic skeletal events and improving health-related quality of life.

Recommendation:
3c. In men with mCRPC and bone pain, radiopharmaceuticals or IV bisphosphonates may be considered for pain palliation.

Qualifying statements for Question 3 recommendations:
• See Table 1-1 for dosages. Patients receiving either denosumab or ZA should be taking 1000 mg of elemental calcium (from dietary and/or supplemental sources) and ≥400 IU of vitamin D daily. The dose of ZA should be reduced in cases of renal insufficiency (creatinine clearance [CrCl] <60 mL/min or serum creatinine [SCr] >132.5 µmol/L). ZA is not recommended below a CrCl of 30 mL/min (or SCr >265 µmol/L). In patients over

the age of 65, CrCl (whether estimated or directly measured) should be used rather than SCr. Denosumab and ZA should not be given in combination.
- There is uncertainty regarding the optimum duration of therapy; with respect to ZA, less-intensive therapy (i.e., every 3 months) may be as effective as monthly treatment (CALGB 70604 Alliance study [19]).
- SRE definitions and data reporting pain are not identical across studies.
- Recommendation 3b applies to men with predominantly bony metastases and no evidence of visceral metastases or large nodal metastases.
- Radiopharmaceuticals can permanently reduce bone marrow reserves, and this should be considered if the patient remains a candidate for palliative cytotoxic chemotherapy. The recommended dose for Ra-223 is one IV injection of 55 kBq/kg of body weight every four weeks for a total of six injections (based on the primary standardization revision for Ra-223 in 2015 by the National Institute of Standards and Technology [20]). The optimal sequencing of Ra-223, denosumab, and bisphosphonates is unclear, and recommendations to patients should be done in consultation with a clinician with expertise in CRPC treatment.
- Systemic therapies for the treatment of mCRPC such as abiraterone/prednisone, enzalutamide, docetaxel, and cabazitaxel have been shown to reduce SREs, improve bone pain and health-related quality of life, and/or improve overall survival in mCRPC. Mitoxantrone has also been shown to improve pain and health-related quality of life (see Guideline 3-15: Systemic Therapy in Men with Metastatic Castration-Resistant Prostate Cancer). The optimal sequencing or combination of these therapies with bone targeted agents is unclear, and recommendations to patients should be done in consultation with a clinician with expertise in CRPC treatment.
- Radiotherapy is one of the main therapeutic approaches to palliate pain in men with bone metastasis [21,22].

QUESTION 4
Can bone-targeted therapies improve overall survival in men with established prostate cancer and bone metastases?

Recommendation:
4. In men with symptomatic mCRPC, Ra-223 is recommended to extend overall survival.
Qualifying statements:
• This recommendation applies to men with predominantly bony metastases and no evidence of visceral metastases or large nodal metastases. • Ra-223 appears to be equally effective whether or not patients have received prior docetaxel or are eligible to receive docetaxel. • Other options are available aside from bone-targeted therapies or radiopharmaceuticals for improving outcomes (see Guideline 3-15: Systemic Therapy in Men with Metastatic Castration-Resistant Prostate Cancer). The optimal sequencing of therapies is unknown. • There is insufficient evidence to support an improvement in overall survival with

bisphosphonates or denosumab in this population.

- Systemic therapies for the treatment of mCRPC such as abiraterone/prednisone, enzalutamide, docetaxel, and cabazitaxel have been shown to reduce SREs, improve bone pain and health-related quality of life, and/or improve overall survival in mCRPC (see Guideline 3-15: Systemic Therapy in Men with Metastatic Castration-Resistant Prostate Cancer). The optimal sequencing or combination of these therapies with bone-targeted agents is unclear, and recommendations to patients should be done in consultation with a clinician with expertise in CRPC treatment.