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Guidelines

Bone Health and Bone-targeted Therapies for Prostate Cancer: a Programme in Evidence-based Care — Cancer Care Ontario Clinical Practice Guideline

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Abstract

Aims: To make recommendations with respect to bone health and bone-targeted therapies in men with prostate cancer.
Materials and methods: A systematic review was carried out by searching MEDLINE, EMBASE and the Cochrane Library from inception to January 2016. Systematic reviews and randomised-controlled trials were considered for inclusion if they involved therapies directed at improving bone health or outcomes such as skeletal-related events, pain and quality of life in patients with prostate cancer either with or without metastases to bone. Therapies included medications, supplements or lifestyle modifications alone or in combination and were compared with placebo, no treatment or other agents. Disease-targeted agents such as androgen receptor-targeted and chemotherapeutic agents were excluded. Recommendations were reviewed by internal and external review groups.
Results: In men with prostate cancer receiving androgen deprivation therapy, baseline bone mineral density testing is encouraged. Denosumab should be considered for reducing the risk of fracture in men on androgen deprivation therapy with an increased fracture risk. Bisphosphonates were effective in improving bone mineral density, but the effect on fracture was inconclusive. No medication is recommended to prevent the development of first bone metastasis. Denosumab and zoledronic acid are recommended for preventing or delaying skeletal-related events in men with metastatic castration-resistant prostate cancer. Radium-223 is recommended for reducing symptomatic skeletal events and prolonging survival in men with symptomatic metastatic castration-resistant prostate cancer.
Conclusions: The recommendations represent a current standard of care that is feasible to implement, with outcomes valued by clinicians and patients.

Key words: Bone mineral density; bone-targeted therapy; denosumab; prostate cancer; radium-223; zoledronic acid

Introduction

There is a growing awareness of bone health issues in men with prostate cancer, together with an absence of evidence-based guidelines to aid clinicians in their

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management. Recently, a number of important studies have been published in both metastatic and non-metastatic prostate cancer. The objective of this clinical practice guideline was to evaluate the effectiveness of therapies targeting bone health across all stages of prostate cancer and to make recommendations with respect to bone health and bone-targeted therapies.

Research Questions

(1) Can therapeutic interventions reduce osteoporosis-related outcomes in men with prostate cancer receiving androgen deprivation therapy (ADT)?
(2) Can therapeutic interventions prevent bone metastases in men with prostate cancer?
(3) Can bone-targeted therapies reduce the incidence of skeletal-related events (SREs), reduce pain or improve quality of life (QoL) in men with prostate cancer metastatic to bone?
(4) Can bone-targeted therapies improve overall survival in men with established prostate cancer and bone metastases?

Materials and Methods

This guideline was undertaken by Cancer Care Ontario's Program in Evidence-based Care (PEBC) at the request of the Genitourinary Cancer Disease Site Group. The PEBC produces evidence-based and evidence-informed guidance documents using the methods of the practice guidelines development cycle [1,2]. This process includes a systematic review of the literature, interpretation of the evidence by the authors, preparation of recommendations, internal review by content and methodology experts and external review by Ontario clinicians and other stakeholders. A detailed description of the methods can be found in [3].

Literature Search

A search for relevant systematic reviews and randomised-controlled trials (RCTs) was conducted in MEDLINE, EMBASE and the Cochrane Library from database inception to January 2016. Study selection and data extraction were carried out by the research methodologist with assistance from the lead authors.

The included studies involved therapies directed at improving bone health in non-metastatic patients or reducing the outcomes associated with prostate cancer metastatic to bone (drug, supplement or lifestyle modification). Studies of anti-cancer therapies (e.g. ADT, abiraterone, enzalutamide and chemotherapeutic agents) were beyond the scope of this guideline.

Results

Recommendations, Qualifying Statements and Key Evidence

Recommendation

(1) For men with non-metastatic prostate cancer at high risk of fracture 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

- See Table 1 for dosages.
- Fracture risk can be estimated based on risk prediction tools such as the World Health Organization Fracture Risk Assessment Tool or the Canadian Association of Radiologists and Osteoporosis Canada tool [4,5].
- Baseline bone mineral density (BMD) testing with conventional dual X-ray absorptiometry is encouraged for men before starting ADT to help determine fracture risk and to identify those individuals who would probably benefit from pharmacological intervention. If a BMD test has been carried out in the past 1–2 years, a repeat test may not be needed before starting ADT unless the patient was initiated on denosumab or a bisphosphonate.
- The optimum duration of therapy is unknown. Current studies provide results up to 36 months of therapy.
- 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 oestrogen receptor modulators. Although both drugs were associated with increased BMD and toremifene reduced the risk of fracture, selective oestrogen receptor modulators are associated with increased risk of venous thromboembolic events, raising safety concerns.
- Three small trials comparing exercise programmes with usual care [6–8] and one small trial comparing group exercise with personal training [9] showed no difference in BMD between groups. One trial showed improvements in QoL measures with exercise [8]. A more comprehensive review of exercise for people with cancer is available [10].
- Men with castration-sensitive prostate cancer (CSPC) and bone metastasis may derive benefit for fracture prevention from starting or continuing denosumab at the osteoporosis-indicated dosage or a bisphosphonate. However, few trials included such men and analyses stratified by the presence or absence of bone metastases were not carried out. Therefore, the evidence of benefit is less compelling in this scenario.