

Practical update for the use of bone-targeted agents in patients with bone metastases from metastatic breast cancer or castration-resistant prostate cancer

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ABSTRACT

Bone metastases are a significant source of morbidity and mortality for patients with breast and prostate cancer. In this review, we discuss key practical themes regarding the use of bone-targeted agents (BTAs) such as bisphosphonates and denosumab for managing bony metastatic disease. The BTAs both delay the onset and reduce the incidence of skeletal-related events (SRES), defined as any or all of a need for radiation therapy or surgery to bone, pathologic fracture, spinal cord compression, or hypercalcemia of malignancy. They have more modest benefits for pain and other quality-of-life measures.

Regardless of the benefits of BTAs, it should always be remembered that the palliative management of metastatic bone disease is multimodal and multidisciplinary. The collaboration of all disciplines is essential for optimal patient care.

Special consideration is given to these key questions:

- What are BTAs, and what is their efficacy?
- What are their common toxicities?
- When should they be initiated?
- How do we choose the appropriate BTA?
- What is the appropriate dose, schedule, and duration of BTAs?

Key Words Bony metastases, bisphosphonates, skeletal-related events, bone-targeted agents, denosumab

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INTRODUCTION

Bone is the most common site of metastasis in many malignancies, including breast (70%), prostate (70%–90%), thyroid (60%), lung (35%), and renal cell carcinomas (35%), and bone metastases can be associated with morbidity and mortality^{1,2}. Since the start of the 2000s, there has been sustained growth in the understanding of the underlying biology of bone metastases and widespread incorporation of inhibitors of osteoclast function—namely, bisphosphonates and receptor activator of nuclear factor κB ligand inhibitors (denosumab)—into clinical practice^{3–5}.

Bone metastases can be either osteolytic, osteoblastic, or mixed, and they most commonly occur in the long bones (femur and humerus) and axial skeleton^{6,7}. These

lesions lead to bone destruction, resulting in significant morbidity and impaired quality of life (QOL). In clinical trials, the efficacy of bone-targeted agents (BTAs) is commonly assessed using the rate of skeletal-related events (SRES), which occur in approximately 27%–40% of patients with metastatic castration-resistant prostate cancer (CRPC) and metastatic breast cancer (mBCa)^{2,8}. Given that SRES and impaired patient QOL are both so important for patient care,

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it is essential that the full range of multimodal and multidisciplinary therapies are readily available for patients^{9–12}.

BTAs FOR METASTASES TO BONE

Types of BTAs

For the purposes of this review, we focus on the two types of BTAs that are approved for use in clinical practice: bisphosphonates and denosumab. Bisphosphonates act primarily as inhibitors of osteoclast activity and have been studied in the management of a variety of malignancies. In oncology, the most commonly used agents are zoledronate and pamidronate. In patients with mBCa and bone metastases, bisphosphonates have been shown to significantly reduce the incidence of SREs, but have not been shown to improve progression-free survival or overall survival^{13–15}. A 2017 meta-analysis showed that bisphosphonates reduce the risk of SREs in advanced breast cancer by 14%¹⁶. Additionally, a Cochrane review concluded that there is some evidence to support modest pain relief associated with the use of bisphosphonates, although current guidelines do not recommend such use exclusively for analgesic purposes^{17,18}. In patients with CRPC metastatic to bone, zoledronate has been shown to reduce SREs by 36%¹⁹.

Denosumab is a fully human monoclonal antibody that acts by inhibiting the receptor activator of nuclear factor κ B ligand, which stimulates the activity and development of osteoclasts, thereby reducing their activity and growth. Denosumab was shown to be superior to zoledronate in patients with bone metastasis from mBCa and CRPC by delaying the onset of first and subsequent SREs^{14,20}. In a meta-analysis of three randomized clinical trials, denosumab reduced the risk of a first SRE by 17% and delayed the time to first SRE by a median of 8.2 months²¹. In one report in patients with mBCa, denosumab, compared with zoledronate, also showed a benefit in health-related QOL measures²².

Treatment Considerations and Toxicities

The toxicities of BTAs are well studied, and bisphosphonates and denosumab all share a number of adverse events, including hypocalcemia, osteonecrosis of the jaw, and atypical femur fractures. Patients who are starting a BTA should receive appropriate calcium and vitamin D supplementation to reduce the risk of hypocalcemia, which occurs more frequently with denosumab (12.4%) than with bisphosphonates (5.3%)^{23,24}. Risk of osteonecrosis of the jaw is rare with either therapy, occurring at rates less than 2% in the first year of treatment²⁵. The risk is higher with denosumab than with bisphosphonates and increases with longer duration of therapy. Dental examination before BTA initiation is recommended by most practice guidelines, and ongoing symptom inquiry is important throughout treatment for prompt identification of this serious adverse event¹⁸.

Bisphosphonates are specifically associated with nephrotoxicity, and renal function must be monitored²⁶. The risk can be reduced by adhering to recommended doses, dosing intervals, and infusion rates as described later in this article²⁷.

When to Initiate Treatment

It is widely accepted practice to initiate treatment with a BTA at first radiographic evidence of bony metastases, because risk of SREs is highest on diagnosis of metastatic disease and within the first year^{18,28,29}. Whether all patients have to commence treatment as soon as there is a radiologic diagnosis has not been investigated. Clinical context should dictate management; in certain situations (for instance, in a patient with a low burden of disease or with visceral metastases and limited life expectancy), delaying the start of a BTA might be more sensible⁴.

Aspects of the pathophysiology of bone lesions have led to some observations in the treatment of osteolytic compared with osteoblastic metastases. Bone metastases in patients with breast cancer are primarily osteolytic, and therefore treatment with inhibitors of osteoclast activity, such as bisphosphonates, is indicated^{13,30}. On the other hand, bone metastases in patients with prostate cancer are primarily osteoblastic, leading to the deposition of calcium in new bone. The rationale for the use of bisphosphonates in the treatment of patients with prostate cancer comes from studies showing that abnormal osteoblastic bone formation is associated with osteoclastic bone resorption and an elevation in osteoclastic markers^{31,32}. Multiple randomized trials have shown significant reductions in the frequency of SREs in patients with bone metastases from a variety of solid tumours that are treated with an osteoclast inhibitor; the use of such agents is therefore recommended for most patients with bone metastases from solid tumours, regardless of whether those metastases are osteolytic or osteoblastic^{15,33–35}.

Choice of Agent and Dosing Schedule

The choice of BTA depends on a number of factors, including tumour site, patient comorbidities, and cost-effectiveness. In mBCa, a joint guideline from the American Society of Clinical Oncology and Ontario Health (Cancer Care Ontario) does not recommend one BTA over another¹⁸. Although denosumab might be preferred based on its associated SRE reduction and its subcutaneous route of administration, those benefits have to be balanced against its significantly higher drug acquisition cost. In a cost-effectiveness analysis, zoledronate given every 3 months was shown to be substantially more cost-effective than monthly denosumab in reducing SREs³⁶.

If a bisphosphonate is selected, zoledronate has the greatest demonstrated efficacy³⁷. The joint 2017 guideline from the American Society of Clinical Oncology and Ontario Health (Cancer Care Ontario) for mBCa recommends the use of zoledronate at a dose of 4 mg given intravenously over no less than 15 minutes¹⁸. Pamidronate 90 mg given intravenously also has demonstrated efficacy in reducing the risk of SREs in mBCa and would be a reasonable option, but it does have a longer infusion time (2 hours)³⁸. In contrast, pamidronate did not demonstrate any benefit over placebo in the treatment of bony metastases from CRPC³⁹. A 2017 Genitourinary Disease Site Group guideline from Ontario Health (Cancer Care Ontario) recommended denosumab or zoledronic acid for preventing or delaying SREs in men with metastatic CRPC^{40,41}.

In terms of dosing schedule, despite the fact that the half-life of bisphosphonates and bone turnover biomarkers exceed 1 year, the dosing interval has historically been more frequent, to coincide with every-3-weeks chemotherapy schedules⁴². Less-frequent dosing of BTAs in breast and prostate cancer is supported by data from three randomized controlled studies. In a meta-analysis, SRE rates in patients with mBCa were similar for zoledronate given every 12 weeks or every 3–4 weeks, regardless of whether patients started on standard dosing (every 3–4 weeks) or de-escalated dosing (every 12 weeks)⁴³. A more recent trial evaluating the noninferiority of 12-weekly compared with 4-weekly dosing for BTAs in patients with breast cancer and CRPC showed that a dose–de-escalated schedule can also be applied to pamidronate⁴⁴.

Currently, the recommended dose and schedule for denosumab is 120 mg administered subcutaneously every 4 weeks^{4,18}. Denosumab has also been tested in a dose–de-escalated schedule. A recent trial that evaluated the noninferiority of 12-weekly compared with 4-weekly dosing for BTAs suggested that the same dose–de-escalated schedule could also be applied to denosumab⁴⁴. To direct future treatment recommendations, one ongoing clinical trial is currently comparing 12-weekly with 4-weekly denosumab in patients with mBCa and CRPC^{33,45}. Data so far would suggest that de-escalation of all commonly used

bone agents, including denosumab, to 12-weekly therapy is a reasonable clinical strategy. Table I summarizes the administration schedules and doses for those commonly used agents. Table II shows estimated prices for BTAs in Canada.

Duration of Treatment

American Society of Clinical Oncology guidelines recommend continuing treatment with BTAs indefinitely¹⁸. That recommendation must be balanced against long-term toxicity risks and patient-centred goals of care. Some data suggest that treatment should continue for 6 months at minimum to achieve a demonstrable reduction in the risk of SREs¹⁹.

For patients who experience a SRE while on treatment with a BTA, therapy continuation is recommended to increase the time to a subsequent SRE⁴⁶. One study investigating the benefit of switching from pamidronate to zoledronic acid in patients with high-risk disease did not show any reduction in SREs or QOL and pain scores, and thus switching between bisphosphonates is not recommended⁴⁷.

Treatment with newer anticancer therapies has extended life expectancy in patients with mBCa and CRPC by a number of years. As a result, the question of the duration of BTA use should take into consideration life expectancy, overall burden of disease, and risk of SREs in each individual patient. Most clinical trials have evaluated the use of BTAs

TABLE I Recommended doses and administration schedules for bone-targeted agents

Agent	Indication	Creatinine clearance (mL/min)	Dose (mg)	Route	Schedule	Infusion rate
Zoledronate	mBCa and CRPC	>60	4	Intravenous	Every 12 weeks or every 3–4 weeks ¹⁸	No less than 15 minutes
		50–59	3.5			
		40–49	3.3			
		30–39	3			
		<30	Use not recommended			
Pamidronate	mBCa only	>90	90	Intravenous	Every 3–4 weeks; may consider every 12 weeks ¹⁸	No less than 2 hours; 4 hours recommended
		30–90	90			
		<30	Use not recommended			
Denosumab	mBCa and CRPC	NA	120	Subcutaneous	Every 3–4 weeks; may consider every 12 weeks ³⁶	NA

mBCa = metastatic breast cancer; CRPC = castration-resistant prostate cancer; NA = not applicable.

TABLE II Estimated price for bone-targeted agents in Canada

Agent	Dose (mg)	Route	Schedule	Infusion rate	Price (CA\$)	
					Per dose ^a	Total annual
Zoledronate	4	Intravenous	Every 3–4 weeks	No less than 15 minutes	335.40 ^b	4,024.80
					415.56 ^c	4,986.70
Pamidronate	90	Intravenous	Every 3–4 weeks	No less than 2 hours	86.78 ^d	3,124.08
Denosumab	120	Subcutaneous	Every 3–4 weeks	NA	575.75	6,909.00

^a Per-dose prices represent a single infusion or injection per the Ontario Drug Benefit Exceptional Access Formulary, October 2015. Drug cost might be reimbursed through the Ontario Drug Benefit Plan. Drug prices are dynamic; thus, the prices listed here might not reflect current prices.

^b Zoledronic acid (Taro Pharmaceuticals, Brampton, ON).

^c Zoledronate (JAMP Pharma Corporation, Boucherville, QC).

^d 10 mL Vial, 3 mg/mL injection (Pfizer Canada ULC, Kirkland, Québec)

NA = not applicable.

for only a maximum of 2 years, and hence no high-quality evidence to support their use beyond 2 years has been developed^{33–35}. Duration of use is currently being further evaluated in a series of Canadian studies.

SUMMARY

Bone-targeted agents are an integral component of the palliative management of bony metastatic disease in mBCa and CRPC. Knowledge of the available agents and their role in the treatment of patients with bony metastases is essential for general practitioners in oncology. The BTAs have demonstrated efficacy in reducing the risk of SRES and in modestly improving pain and other QOL outcomes. However, it is important to remember that BTAs have no effect on either progression-free or overall survival, and they have significant associated toxicities and costs. Further areas of study include clarifying the optimal dose, schedule, and duration of treatment for these agents.

We recommend the use of BTAs to reduce the risk of SRES for most patients with bone metastases from solid tumours. For patients with a minimal bone tumour burden or limited expected survival, treatment with a BTA should be discussed and individualized. We advise that the use of BTAs be specifically applied to CRPC with bone metastases. In the absence of excessive toxicity, and if within the patient's and the clinician's joint treatment goals, BTAs should be continued indefinitely.

Key Points

- Bisphosphonates and denosumab are osteoclast inhibitors that are recommended for the treatment of bony metastases in patients with breast cancer and CRPC.
- Treatment with a BTA can be considered at the first evidence of bony metastasis.
- Before therapy begins, guidelines recommend that patients undergo dental examination because of a risk—albeit low—of osteonecrosis of the jaw. Supplementation with vitamin D and calcium should also be initiated.
- If initiating a bisphosphonate, a dose-de-escalated schedule of administration every 12 weeks can be used. If initiating denosumab, the current recommendation is for administration every 4 weeks. However, the results of ongoing clinical trials suggest that a 12-weekly schedule of denosumab is reasonable.
- Bone-targeted agents may be continued beyond the 2 years evaluated in clinical trials. However, given the possibility that their toxicities might outweigh their benefits with longer duration of use, ongoing clinical trials are evaluating this approach.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology's* policy on disclosing conflicts of interest, and we declare the following interests: RF has consulted for Novartis, Janssen, Merck, Pfizer, and Bayer. All other authors have no conflicts of interest to disclose.

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