Weighing Bone-targeted Treatment Options for Patients with Solid Tumours and Skeletal Complications from Metastatic Disease

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Abstract

The complications of metastatic bone disease (MBD) in advanced cancer, especially skeletal-related events (SREs), are a significant cause of morbidity that can seriously impair the quality of patients' lives. Treatments that prevent SREs, reduce or delay the onset of pain and preserve function and activities of daily living are central to good patient care. In this article, we discuss results from clinical trials that show the relative benefits and harms of different bone-targeted agents, which may be given orally, intravenously or subcutaneously. These data, when considered alongside various patient characteristics, can provide oncologists with better opportunities to individualise care. Optimal management with treatments that enhance efficacy and adherence mean that clinicians can improve the outlook for their patients with MBD, who may consequently experience fewer SREs and less pain and enjoy a better overall quality of life.

Keywords

Metastatic bone disease, bone metastases, advanced cancer, bisphosphonates, denosumab, RANK ligand, osteoclast, bone resorption, clinical trials

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Approximately 70–80 % of patients with advanced prostate or breast cancer and 30–40 % of patients with advanced lung cancer and other solid tumours develop metastatic bone disease (MBD).[1] The added burden to patients once cancer afflicts bone is significant. In addition to the reduced survival associated with bone metastases, systemic morbidity such as bone pain is common.[1] Other complications directly related to metastatic bone destruction include: pathologic fracture, spinal cord compression, that can result in numbness or weakness, urinary or faecal incontinence or paralysis, and hypercalcaemia of malignancy.[1] All these problems can have a deleterious impact on the quality of patients' lives. Irradiation of the bone (e.g., for bone pain or fracture), surgery to the bone to prevent or treat fracture, pathologic fractures and spinal cord compression are conditions labelled collectively as skeletal-related events (SREs).[2] While the term SRE is commonly used to quantify the effects of MBD, additional symptoms from disease in the skeleton, such as pain and impaired mobility, can occur irrespective of the presence of SREs.

Indeed, prognosis is diminished for patients with MBD who develop SREs compared with those who do not.[2,3] Furthermore, the overall cost of the treatment of SREs places a significant burden on healthcare systems.[4–7] In addition to appropriate systemic antitumour therapy to palliate symptoms and prolong life-expectancy, delaying or preventing SREs with bone-targeted agents is important. A key approach is the use of drugs to reduce osteoclast-mediated bone destruction (see *Table 1*).[8–11]

A number of agents classified as bisphosphonates bind to bone and are toxic to osteoclasts, reducing their bone-resorbing effects and thereby decreasing SREs. Bisphosphonates vary in their mode of administration, but also in their degree of potency, toxicity and effectiveness according to tumour type. For example, clodronate is administered orally, ibandronate is available in both oral and intravenous formulations, and pamidronate and zoledronic acid are both administered intravenously. The amino-bisphosphonates

(ibandronate, pamidronate, zoledronic acid) are considered more potent than earlier generation drugs such as clodronate and have different side-effect profiles. While approvals by cancer type are country- and region-specific, ibandronate, clodronate and pamidronate have demonstrated efficacy in patients with metastatic breast cancer and bone lesions from multiple myeloma. Zoledronic acid is approved to prevent SREs (including tumour-induced hypercalcaemia) in patients with advanced malignancies involving bone.

The newest bone-targeted therapy, denosumab, is a fully human monoclonal antibody with high affinity and specificity for the signalling protein RANK ligand (RANKL). Denosumab prevents the interaction of RANKL with its RANK-binding site on the surface of osteoclasts. This reduces osteoclast formation, function and survival, inhibiting osteoclast-mediated bone destruction dramatically.[12,13] Unlike bisphosphonates, denosumab is administered by subcutaneous injection and has proven more effective than zoledronic acid in preventing SREs in patients with bone metastases from solid tumours.[14–16] Denosumab is not indicated in Europe for the prevention of SREs in patients with multiple myeloma.

In this paper, we review the currently available treatments and their efficacy in relation to reducing skeletal complications from MBD. We also consider comparative treatment characteristics that may help to maintain, rather than impede, a good quality of life, and summarise the relative advantages and disadvantages of different treatments based on patient-centred attributes. In order to provide focused and in-depth discussion, this article addresses only MBD from solid tumours, not from multiple myeloma.

Considering Efficacy and More

As more cancer treatments now prolong both progression-free and overall survival, there is an increasing need to ensure that patients' health-related quality of life (HRQoL) is optimally maintained as well.[17] When choosing between treatment possibilities for advanced cancer, patient preferences should be taken into account. Clinicians and patients can together evaluate the advantages and disadvantages of the different options based on factors beyond treatment efficacy. Clinicians tend to focus more on disease-related factors (such as previous therapies and response, tumour burden and the need for rapid disease or symptom control[18]), whereas patients tend to place greater emphasis on HRQoL (including burden of treatment, treatment side effects and impact on their lifestyle and family) and on the tangible and intangible costs of treatment.[19] These more psychosocial issues are often difficult to quantify, but their consideration can provide valuable guidance when clinicians discuss the various treatment options available with individual patients. HRQoL-related factors can not only aid optimal decision-making, but can also improve physician–patient communication, which may lead to better outcomes for some cancer patients.[20]

The issues beyond efficacy that merit discussion include details about the mode and frequency of administration, availability of therapy, the relative acceptability of side effects and, in some healthcare systems, funding for the agent. Other factors important to patients include their own out-of-pocket costs – incurred through travel and time for extra testing or monitoring – and the added financial burden that might be sustained by care-givers. *Table 2* summarises the various features that may influence adherence to and effectiveness of treatment. It is divided into three parts:

Table 1: Approved Bone-resorptive Therapies in Europe

Therapy	Approved Indications in Europe	Dosing and Schedule	Mode of Administration	Type of Malignancy
Denosumab (XGEVA®)[75]	Prevention of skeletal-related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with bone metastases from solid tumours	Single 120 mg injection every 4 weeks	Subcutaneous	Breast, prostate and other cancers
Zoledronic acid (Zometa®)[73]	Prevention of skeletal-related events (pathological fractures, radiation to bone, spinal cord compression, surgery to bone or tumour-induced hypercalcaemia) in patients with advanced malignancies involving bone Treatment of tumour-induced hypercalcaemia	Single 4 mg infusion over 15 minutes minimum every 3–4 weeks; dose reduction or withholding based on renal function. Single 4 mg infusion over 15 minutes minimum	Intravenous	Breast, prostate and other cancers; multiple myeloma
Pamidronate (Aredia®)[83]	Treatment of osteolytic bone metastases of breast cancer and osteolytic lesions of multiple myeloma, in conjunction with standard antineoplastic therapy Treatment of moderate or severe hypercalcaemia associated with malignancy with or without bone metastases	Single 90 mg infusion every 3–4 weeks Moderate hypercalcaemia: single 60–90 mg infusion over 2–24 hours; severe hypercalcaemia: single 90 mg infusion	Intravenous	Breast cancer; multiple myeloma
Ibandronate sodium (Bondronat®)[74,84]	Tumour-induced hypercalcaemia of malignancy Prevention of skeletal-related events in patients with breast cancer and bone metastases	2–4 mg infusion Intravenous: single 6 mg infusion over 15 minutes minimum every 3–4 weeks for patients with creatinine clearance >50 ml/minute; oral: 50 mg daily	Intravenous Intravenous or oral	Breast cancer
Clodronate (Bonefos®)[85]	Management of osteolytic lesions, hypercalcaemia and bone pain associated with skeletal metastases in patients with carcinoma of the breast or multiple myeloma Maintenance of clinically acceptable serum calcium levels in patients with hypercalcaemia of malignancy initially treated with an intravenous bisphosphonate	Single 1,600 mg daily dose Up to 3,200 mg daily divided in doses >1,600 mg taken separately	Oral	Breast cancer; multiple myeloma

- treatment characteristics;
- efficacy (and comparative efficacy when available); and
- notable side effects and their management.

Treatment Characteristics

In the context of treating advanced cancer, factors such as ease of medication use and accessibility of treatment may often be considered as secondary or tertiary matters. However, these can be of primary concern to patients, and discussing them may help guide treatment choices. Patients who cannot easily travel to treatment centres on a regular basis, whether due to physical distance, poor health or lack of someone to transport them, may prefer oral treatment. Those who have problems with intravenous access, whether from previous extensive intravenous treatment, anatomical limitations or complications of an intravenous catheter (such as infection), may well favour oral or subcutaneous administration. Many view the oral route as a more convenient mode of administration,[21] but, as cancer affects older people, co-morbidities in these patients demand polypharmacy. Patients who need to ingest large quantities of oral medications, including as part of their ongoing cancer treatment, may not find the addition of yet another oral drug very desirable. Those experiencing difficulties adhering to the stringent requirements associated with oral bisphosphonate regimens, such as remaining upright and abstaining from food or drink for one hour, may prefer intravenous or subcutaneous options. These last options also have less frequent dosing schedules (e.g., every three to four weeks), which could be seen as attractive compared with daily administration of oral drugs.[22]

Not all intravenous formulations of bone-targeted agents are the same and considering their differences may influence the choice of treatment. The shorter infusion time of 15 minutes minimum with zoledronic acid and ibandronate (for patients with creatinine clearance [CRcl] >50 ml/min) has been noted as an advantage over pamidronate, which is infused over two hours minimum.[23] In practice, studies find that the administration of zoledronic acid is typically longer than 15 minutes, as the need for renal monitoring, ancillary pre-infusion tasks and patient hydration place a greater time burden on patients and clinicians alike.[23–25] A clinic-based study in the US reported mean zoledronic acid infusion times of 34 minutes for breast cancer and 29 minutes for prostate cancer, with total administration times (including ancillary and hydration tasks) of 72 and 65 minutes, respectively.[25] Less frequent administration of intravenous bisphosphonates – every 12 weeks instead of every three to four weeks – is being explored to reduce costs and toxicity, although efficacy has not been established with less frequent dosing regimens.[26,27]

Subcutaneous administration of denosumab is expected to be less burdensome than intravenous administration of a bisphosphonate. Unfortunately, this aspect of quality of care could not be assessed in the denosumab versus zoledronic acid comparative SRE trials due to their double-dummy, double-blind study designs. Patient preferences for subcutaneous versus oral therapy, or for intravenous versus oral therapy, have been assessed between bisphosphonates[28] and in other therapeutic areas.[29–31] A hypothetical preference study in the UK, with healthy volunteers evaluating subcutaneous injections versus intravenous infusions of bone-modifying agents, suggested that respondents perceived inconveniences with either type of treatment, but still preferred subcutaneous injections to intravenous infusions as indicated by significant differences in mean health state utilities.[32]

More work in this area, taking preferences of real patients into account, is warranted, as research on the subject was done before the development of subcutaneous routes of administration and hence considers only oral and intravenous experiences.[22]

Cost of Treatment

The cost of bone-targeted treatment affects patients as it can determine whether a therapy is available for clinicians to prescribe. Factors on which costs are based vary among countries and among healthcare systems; health technology appraisals may to varying degrees – or may not – include costs associated with: the burden of illness, effectiveness of treatment, the drug and its administration, renal monitoring requirements and regimen compliance. Comparing the cost-effectiveness of all available treatments can be difficult, as can indirect comparison of cost studies. However, comparative-cost data for denosumab and zoledronic acid based on health economic models are available. Models that assess the cost of treatment over patient lifetime and use clinic-based SRE rates provide relevant cost and outcome estimates. Since denosumab results in fewer SREs and increased quality-adjusted life-years (QALYs – an expression of quality and quantity of life lived), it is considered by some as a more cost-effective treatment for the prevention of SREs than zoledronic acid despite its higher acquisition costs.[33,34] Health technology assessments generally do not take into account the additional hidden costs to patients associated with the illness and its treatment, including lost time at work for both patients and care-givers; these additional costs may weigh in favour of denosumab due to its subcutaneous mode of administration and increased efficacy.

Efficacy

The efficacy of bisphosphonates in delaying cancer-related skeletal complications is influenced by the potency of the bisphosphonate, its bioavailability and patient adherence to treatment. The order from lowest to highest potency is as follows: clodronate, pamidronate, ibandronate and zoledronic acid.[35] Oral formulations are available for clodronate and ibandronate, but their bioavailability is much less than that of bisphosphonates administered intravenously, particularly if they are not taken according to the strict administration instructions.[36,37] All bisphosphonates have a long half-life because they accumulate within bone, where they are incorporated integrally into the bone structure. Despite this long half-life, metabolic activity is a function of the free levels of the drug; hence, the activity of this class of agents in MBD is shortened by the local resorptive drive of the tumour. Also, the risk of skeletal complications after zoledronic acid treatment is a function of persistence of use.[38]

Denosumab shows a bioavailability of >60 %.[39] It is not deposited in bone and its effects are reversible.[40] As with all monoclonal antibodies, denosumab is likely eliminated by the reticuloendothelial system,[41] with no effect on renal function, in contrast to bisphosphonates, which are excreted by the kidneys and are nephrotoxic.[42] Head-to-head comparative trials of denosumab and zoledronic acid showed that denosumab is significantly more effective at reducing the rate of SREs in patients with solid tumours and bone metastases.[43] Among 5,544 patients with breast, prostate or other solid tumours and bone metastasis, denosumab reduced the risk of first on-study SRE by 18 % compared with zoledronic acid, with a delay in the median time to first SRE of 8.3 months with denosumab (time to first SRE 27.7 months) versus zoledronic acid (time to first SRE 19.4 months) (hazard ratio 0.82, 95 % confidence interval [CI] 0.75–0.89; p<0.0001); denosumab

also reduced the risk of any on-study SRE by 19 % compared with zoledronic acid (relative risk 0.81, 95 % CI 0.74–0.88; p<0.0001).[44]

The comparative effectiveness of denosumab and zoledronic acid has also been assessed using a number needed to treat (NNT) analysis. This method describes effectiveness in terms of people who may be affected, rather than a percentage risk reduction. A lower NNT represents a more beneficial treatment outcome. NNT analyses between denosumab and zoledronic acid demonstrated a greater treatment benefit with denosumab across tumour types: treatment of seven patients with denosumab would prevent an additional SRE per year in patients with breast cancer metastatic to bone[45] and in patients with other advanced solid tumours,[46] while treatment of five patients with denosumab would prevent an additional SRE per year in patients with castration-resistant prostate cancer metastatic to bone.[47]

Patient-reported Outcomes

The impact that different bone-targeted therapies in MBD patients with advanced cancer have on pain is important. Fear and other psychosocial dimensions of pain should not be overlooked.[48,49] Results from a plethora of studies investigating the effects of bisphosphonates on bone pain across cancer sites have been summarised in systematic reviews.[50–52] The balance of evidence indicates that oral clodronate has little effect on bone pain in metastatic breast cancer, whereas both oral and intravenous ibandronate have produced significant reductions compared with placebo.[50] Intravenous pamidronate improved pain scores compared with placebo[53] and also improved pain scores compared with oral clodronate over three months of treatment in a small comparative trial in breast cancer.[54]

Zoledronic acid, compared with placebo, has been found to attenuate pain worsening in metastatic prostate cancer[55,56] and reduce pain in patients with breast cancer.[57] In the head-to-head trials of denosumab and zoledronic acid in breast cancer, prostate cancer and other solid tumours, denosumab was more effective at delaying the onset of significant pain, particularly in patients with no or mild pain at initiation of treatment. In these patients, denosumab reduced the risk of pain worsening to moderate or severe compared with zoledronic acid by 22 % in breast cancer (p=0.0024), 11 % in prostate cancer (p=0.14) and 19 % in other solid tumours (p=0.050), with median delays in pain worsening of one to four months depending on tumour type.[58–60] Denosumab and zoledronic acid were similarly effective in palliating pain.

Some bone-targeted therapies have been found to influence analgesic use for pain relief. A German clinic-based study of breast cancer patients found that, with ibandronate therapy, more patients ceased taking analgesics and fewer patients required more potent analgesia by the end of the study than at enrollment.[61] Analyses of data pooled from oral and intravenous clodronate trials in solid tumours found an increased proportion of patients requiring less analgesia at four and 12 weeks compared with patients receiving placebo.[52] The comparative denosumab and zoledronic acid trials across advanced cancers collectively showed that fewer denosumab-treated patients reported shifts from no or low analgesic use at baseline to strong opioid-level analgesic use by study end.[62]

The direct effects of bone-targeted agents on general measures of patients' HRQoL can be challenging to quantify, but some improvement in overall HRQoL has been observed in the breast cancer setting. Statistically significant improvements in overall HRQoL have been reported with both oral and intravenous ibandronate, but not with other bisphosphonates.[51] A greater proportion of denosumab-treated patients compared with zoledronic acid-treated patients reported clinically meaningful improvements in HRQoL in the comparative trial in breast cancer.[63]

Notable Side Effects

The most troubling adverse effects with oral bisphosphonate regimens are oesophagitis and gastrointestinal irritation, which can negatively impact treatment adherence.[64] Rates of gastrointestinal disorders are estimated to be 57 % with oral clodronate versus 45 % with placebo[64,65] and 15 % with oral ibandronate versus 8 % with placebo.[66] The most common adverse events with intravenous bisphosphonates are acute phase reactions, such as fever, chills and muscle aches, after the initial infusion.[67] While fever can occur in over 50 % of patients after their first dose,[57] overall symptoms are temporary, generally mild and managed effectively with anti-inflammatory drugs. However, patients who experience severe acute phase reactions after receiving their first bisphosphonate dose may be inclined to interrupt treatment.[68]

The potential for increased nephrotoxicity is of concern with both oral and intravenous bisphosphonates, as these agents are eliminated via the kidneys and, when used in higher doses or infused rapidly, can induce renal impairment in patients with previously normal renal function.[55] The type of bisphosphonate and differences in half-life, protein binding capacity, dosing, schedule of administration and duration of infusion affect the occurrence and severity of renal toxicity. For instance, the long half-life of zoledronic acid in renal tissue of 150–200 days[69] may contribute to greater cumulative toxicity compared with ibandronate, which has a half-life in renal tissue of 24 days in animal models.[70,71] Patients require monitoring of serum creatinine levels before administration of each dose, and intravenous bisphosphonate dosing and/or infusion rate may require adjustments based on CRcl.[42,72] Bisphosphonates have to be withheld until serum creatinine levels recover sufficiently.[73] Bisphosphonates are not recommended for patients with severe renal impairment (CRcl <30 ml/minute),[73] with the exception of ibandronate, which, per the label, can be administered at a reduced dose in patients with CRcl <30 ml/minute.[74]

Denosumab, which is not associated with renal toxicity, does not require renal monitoring or dose adjustment, nor does it have to be withheld from patients with renal dysfunction.[75]

As expected for agents that inhibit bone resorption and the associated calcium release from bone, decreases in serum calcium levels can occur with both denosumab and zoledronic acid. In the comparative trials of denosumab and zoledronic acid, the incidence of hypocalcaemia was generally low, but more frequent with denosumab than with zoledronic acid across solid tumours (9.5 % versus 4.8 %, respectively, in integrated analyses in patients with solid tumours only).[44] In the post-marketing setting, cases of severe hypocalcaemia (including rare symptomatic cases) have been reported in patients receiving zoledronic acid[76] or denosumab,[75] and rare fatal cases of severe hypocalcaemia have been reported in patients receiving denosumab who had advanced metastatic cancer and other concurrent medical conditions;[75] the patients receiving

Table 2: Cross-therapy Assessment of Bone-targeted Treatments by Characteristics, Efficacy and Notable Side Effects

	Clodronate[85]	Ibandronate[74] (Oral Formulation)	Ibandronate[84] (Intravenous Formulation)	Pamidronate[83]	Zoledronic acid[73]	Denosumab[75]
			Treatment Characteristics			
Mode of Administration	Oral	Oral	Intravenous	Intravenous	Intravenous	Subcutaneous
Frequency	Once daily unless dose >1,600 mg	Once daily	Once every 3–4 weeks	Once every 3–4 weeks	Once every 3–4 weeks	Once every 4 weeks
Travel to Clinic	Not required	Not required	Usually required	Usually required	Usually required	Not required (administration by healthcare professional at home possible)
Recommended Duration of Treatment	Begin treatment following diagnosis of bone metastasis; optimal treatment duration unknown; ASCO guidelines recommend that bone-targeted agents be continued until evidence of substantial decline in a patient's general performance status (based on clinical judgment)[11]					
Administration	Take on empty stomach, preferably in the morning; except for plain water, no food or drink for 2 hours before and 1 hour after dose; avoid drinking milk in this period	Take whole after overnight fasting and before first food or drink of the day; continue fasting for 30 minutes minimum afterwards (plain water allowed); stand or sit upright and do not lie down for 60 minutes afterwards; avoid taking other medicines/ supplements beforehand	Intravenous administration capabilities required; 2-hour infusion recommended for pamidronate; zoledronic acid requires 15 minutes minimum infusion time			Injection in the upper arm, upper thigh or abdomen
Other Considerations	Use with caution in patients with renal failure; daily doses exceeding 1,600 mg should not be used continuously	Adjust dose in case of renal impairment; moderate renal impairment (CRcl ≥30 and <50 ml/min): one 50 mg tablet every second day; severe renal impairment (CRcl <30 ml/min): one 50 mg tablet every week; treatment contraindicated if hypocalcaemia present	Adjust dose for renal impairment; moderate renal impairment (CRcl ≥30 and <50 ml/min): 4 mg infused over 1 hour; severe renal impairment (CRcl <30 ml/min): 2 mg infused over 1 hour	Withhold treatment in event of renal deterioration; resume only when creatinine returns to within 10 % of baseline	Reduce dose in patients with renal impairment; co-administer oral calcium (500 mg) and vitamin D (400 IU) daily	Pre-existing hypocalcaemia must be corrected prior to initiating therapy
			Treatment Efficacy			
Breast Cancer	Reduced overall skeletal morbidity* by 26–27 % versus placebo[86,87]	Reduced risk of new bone events** by 38 % versus placebo[66]	Reduced risk of new bone events** by 38 % versus placebo[88]	Proportion of women developing skeletal events (excluding HCM) was 51 % with 90 mg pamidronate and 64 % with placebo; median time to first skeletal event was 12.7 months with pamidronate and 7 months with placebo[53]	Denosumab 120 mg reduced time to first SRE by 18 % and risk of total number of SREs by 23 % compared with ZA 4 mg[16]	

Table 2 Continued: Cross-therapy Assessment of Bone-targeted Treatments by Characteristics, Efficacy and Notable Side Effects

	Clodronate[85]	Ibandronate[74] (Oral Formulation)	Ibandronate[84] (Intravenous Formulation)	Pamidronate[83]	Zoledronic acid[73]	Denosumab[75]
			Treatment Efficacy			
Breast Cancer				No significant difference in the proportion of women developing skeletal events (excluding HCM) with pamidronate 90 mg (45 %) and ZA 4 mg (43 %); in subgroup of patients with lytic lesions, ZA 4 mg significantly prolonged time to first skeletal event compared with pamidronate 90 mg (median 310 versus 174 days, respectively; p=0.013)[89]		
Prostate Cancer	NA	NA	NA	No difference in proportion of patients developing an SRE between pamidronate 90 mg and placebo[82]	Denosumab 120 mg reduced risk of time to first SRE by 18 % and risk of total number of SREs by 18 % compared with ZA 4 mg[14]	
All Solid Tumours Combined	NA	NA	NA	NA	Denosumab 120 mg reduced time to first SRE by 17 % and risk of total number of SREs by 18 % compared with ZA 4 mg[43]	
			Notable Treatment Side Effects			
Acute Phase Reactions (Fever, Muscle Ache and Rigor)			Fever occurs in up to 55 % of patients; symptoms, including chills and muscle aches, typically occur within 12 hours after initial infusion; symptoms are mild and transient; unnecessary to switch to another drug or discontinue therapy Management: symptoms easily relieved by anti-inflammatory agents[72]			
Gastrointestinal Toxicity	Oesophagitis, diarrhoea, gastric irritation[64,72]					
Hypocalcaemia			Occurs rarely (2–6 %); may be observed in patients with pre-existing imbalance or those simultaneously taking particular medications, such as interferon;[72] severe hypocalcaemia, including rare symptomatic cases, reported post-marketing[76] Prevention/management: baseline assessment of 25-hydroxy vitamin D before initiating treatment; correct pre-existing hypocalcaemia prior to initiation; calcium/vitamin D supplements encouraged[72,90]			Rate of hypocalcaemia was 9.6 % with denosumab versus 5.0 % with ZA in clinical trials; severe hypocalcaemia, including symptomatic cases, reported post-marketing[75,76] Prevention/management: correct pre-existing hypocalcaemia before initiating treatment; supplementation with calcium and vitamin D unless hypercalcaemia present[75]
Renal Toxicity (Increase in Serum Creatinine from Baseline)				Incidence related to dose, schedule, duration of administration and concomitant medications; use cautiously in elderly patients[72] Prevention/management: assess serum creatinine before each treatment; lower starting dose according to prescribing guidelines[81]		
Osteonecrosis of the Jaw	Uncommon: incidence was 1.3 % with ZA and 1.8 % with denosumab in head-to-head comparative trials;[77] pre-existing dental conditions and duration of treatment may increase risk. Prevention/management: encourage dental hygiene, proactively monitor dental health;[81] can usually be managed with antibiotics and superficial debridement[77]					

** Skeletal morbidity defined as cumulative number of events (hypercalcaemia, course of radiation therapy to bone, fracture). ** Bone events included vertebral fractures, pathologic non-vertebral fractures and radiotherapy or surgery for bone complications.*
ASCO = American Society of Clinical Oncology; CRcl = creatinine clearance; HCM = hypercalcaemia of malignancy; NA = not applicable; IU = international unit; SRE = skeletal-related event; ZA = zoledronic acid.

denosumab were also taking a variety of other concurrent medications, including anticancer therapies; it is not known if the concurrent conditions and therapies contributed to the hypocalcaemia or the fatal outcomes in these patients.

Pre-existing hypocalcaemia must be corrected prior to initiating bone-targeted therapy, and it is important that clinicians advise their patients to take calcium and vitamin D supplements during treatment. Patients with significant renal dysfunction (CRcl <30 ml/min) or who are on active dialysis are at increased risk of hypocalcaemia. Thus, when initiating bone-targeted therapy in these patients, it may be prudent to plan more frequent monitoring of calcium levels.

Osteonecrosis of the jaw (ONJ) occurs with very low frequency but can be a serious adverse event with both denosumab and intravenous bisphosphonates. Among 5,723 patients in the denosumab versus zoledronic acid comparative trials, where ONJ was independently adjudicated, ONJ occurred in 1.6 % of patients overall (1.8 % receiving denosumab and 1.3 % receiving zoledronic acid; p=0.13); over half of these cases were treated conservatively.[77] Symptoms of this adverse event can include swelling and numbness, pain, infection or drainage in the jaw. Conservative management of ONJ is generally recommended using antibiotics, oral rinses and limited debridement. Aggressive treatment by surgery and bone resection is only required in patients with severe manifestations of the condition.[78,79] The most common risk factors leading to ONJ in patients receiving bisphosphonates or denosumab are pre-existing dental or gum disease and invasive dental procedures such as tooth extraction.[80] Preventive dentistry is recommended prior to initiation of bone-targeted agents in patients with poor oral hygiene or dentition. Clinicians should proactively encourage good dental hygiene practices in their patients to manage ONJ severity or to reduce the risk of ONJ, as it can be preventable.[81]

Although some tumour types, patient features and other considerations will dictate the bone-targeted treatments to be offered (for example, pamidronate is ineffective in prostate cancer[82]), clinicians nevertheless still have large numbers of patients for whom there is a variety of available treatment options.

Discussion

Although the efficacy of bone-targeted therapies is a key factor in the choice of treatment, there are several factors beyond efficacy that are important, as discussed above; clinicians need to tailor the bone-targeted treatment to fit most appropriately with the clinical condition of the patient. All efficacious bone-targeted therapies carry risks of complications, including renal toxicity, ONJ, gastrointestinal irritation and hypocalcaemia; some of these are predictable (e.g., ONJ is more likely in patients with poor oral hygiene or who are undergoing dental extractions) and some can be prevented. If the patient's pre-existing renal function is impaired, or if the patient is receiving other treatments that increase the risk of renal toxicity, this might further influence the choice of bone-targeted treatment.

Although oral drugs are perceived as convenient, especially for patients who have difficulty travelling to the cancer centre or live in remote locations, they may be less effective than other options and complete treatment adherence cannot be assumed. Asking about concomitant medications and patients' ability to swallow a large number of medications may quickly reveal that intravenous or subcutaneous formulations might be better than an oral one. Some clinicians may feel that, for certain individuals with characteristics that limit the use of bone-targeted drugs, other available therapies – e.g., radionuclides or focal radiotherapy – may be more appropriate to provide some palliation.

The actual cost of the drug and associated administration costs cannot be ignored. Some clinicians who practice in low-income countries, or in countries where access to novel therapies is determined by the thresholds permitted following a health technology assessment, may find it difficult to obtain access to the most efficacious or convenient drugs. Oral preparations are cheaper than intravenous formulations, but intravenous zoledronic acid is more effective than any of the other bisphosphonates given either orally or intravenously. The accumulating data from pivotal trials showing the superior efficacy of denosumab over zoledronic acid in solid tumours mean that this treatment option should be considered.[14–16] Patients are increasingly better educated regarding their disease and will learn about treatment options from a variety of sources, including the Internet. Therefore, discussing all potentially available treatments is important to avoid patients' mistrust of clinicians. Burden and costs to care-givers associated with different treatments also need attention. Repeated monthly visits to a doctor's surgery or cancer centre for intravenous treatment and monitoring have financial consequences for families. Oral and subcutaneous formulations may circumvent the expenses and practical difficulties of travelling to the clinic; denosumab, for example, can be administered by a healthcare professional in the patient's home.

Finally, the preservation of functionality and quality of life is central to the care of patients with MBD. With the various bone-targeted agents now available, oncologists have the opportunity to individualise and optimise the care of their patients. By choosing treatments that enhance efficacy and adherence, clinicians can improve the outcomes for their patients, who may consequently experience fewer serious SREs and less pain and enjoy a better overall quality of life. ■

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