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Management of bone health in solid tumours: From bisphosphonates to a monoclonal antibody

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ABSTRACT

Patients with solid tumours are at risk of impaired bone health from metastases and cancer therapy-induced bone loss (CTIBL). We review medical management of bone health in patients with solid tumours over the past 30 years, from first-generation bisphosphonates to the receptor activator of nuclear factor κB ligand (RANKL)-targeted monoclonal antibody, denosumab. In the 1980s, first-generation bisphosphonates were shown to reduce the incidence of skeletal-related events (SREs) in patients with breast cancer. Subsequently, more potent second- and third-generation bisphosphonates were developed, particularly zoledronic acid (ZA). Head-to-head studies showed that ZA was significantly more effective than pamidronate for reducing SREs in patients with breast and castrate-resistant prostate cancer (CRPC), becoming the standard of care for more than a decade. The RANKL inhibitor denosumab was licensed in 2010, and head-to-head studies and integrated analyses confirmed its superiority to ZA for preventing SREs, particularly in breast cancer and CRPC. Bisphosphonates and denosumab have also been investigated for prevention of CTIBL in patients receiving hormonal therapy for breast and prostate cancer, and denosumab is licensed in this indication. Despite advances in management of bone health, several issues remain, notably the optimal time to initiate therapy, duration of therapy, and dosing frequency, and how to avoid toxicity, particularly with long-term treatment. In summary, introduction of ZA and denosumab has protected patients with bone metastasis from serious bone complications and improved their quality of life. Ongoing research will hopefully guide the optimal use of these agents to help maintain bone health in patients with solid tumours.

Introduction

Bone health is an important consideration in patients with solid tumours, as both metastasis to bone and cancer therapy-induced bone loss (CTIBL) can increase morbidity and reduce quality of life [1,2]. Bone is a common site of metastasis in patients with cancer, with prostate, breast and lung the most frequent tumours leading to bone metastasis, accounting for 34%, 22% and 20% of cases, respectively [3]. A recent study in patients with solid tumours in the USA estimated the incidence of bone metastases in patients with solid tumours to be 6.9% at 5 years after diagnosis and 8.4% at 10 years [4], while a meta-analysis of 156 studies in breast cancer found that a median of 12% of patients with stage I–III breast cancer developed bone metastases during a median follow-up period of 60 months [5]. The incidence of bone metastasis is, however, difficult to estimate, with most studies generally based on clinical records and autopsy data, and so may not reflect current treatment patterns [4]. The true incidence of bone metastasis is, therefore, unknown [2]. Metastasis begins when cancer cells escape from the primary tumour and enter the circulation [1,2,6]. These circulating cancer cells have affinities for specific tissue types, such as bone – this is known as the 'seed and soil' hypothesis. When circulating cancer cells infiltrate bone, a vicious cycle is triggered in which signalling between cancer cells and bone cells leads to the development of the metastatic lesion [1,6]. Bone metastases can be broadly classified as osteoclastic, characterised primarily by destruction of normal bone, and osteoblastic, characterised by deposition of new

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bone [2].

Bone metastases are a major cause of morbidity, including skeletal-related events (SREs, usually defined as fracture, spinal cord compression, need for radiation therapy or surgery, and less often tumour-related hypercalcaemia, although exact definitions can vary between clinical trials), severe pain, impaired mobility, and bone marrow aplasia [2]. Pathologic fractures occur in 10–30% of all cancer patients, with higher rates in some cancers such as multiple myeloma (up to 37%) and breast cancer (up to 52%) [7,8]. Such fractures occur most frequently in the ribs and vertebrae. As a result, bone metastases have a substantial impact on patients' quality of life and contribute to increased healthcare costs [1,2,6,9–11].

The treatment of bone metastases in patients with solid tumours is generally palliative, with very limited opportunities for complete eradication [12]. Bone metastases can be managed with a range of therapeutic modalities, including external beam radiotherapy, endocrine treatments, chemotherapy and radioisotopes, as well as orthopaedic intervention to correct structural complications or nerve compression. These treatments are accompanied by further medical care to prevent fractures and other bone complications using various bisphosphonates and the receptor activator of nuclear factor κB ligand (RANKL)-targeted agent denosumab, which are licensed for the prevention of SREs in patients with bone metastases due to solid tumours (Supplementary Table 1; Fig. 1) [13–48].

In the early 21st century, the potential of bisphosphonates and denosumab was recognised for the management of CTIBL, another bone-related complication experienced by some patients with cancer [49,50]. Oestrogen and testosterone have both direct and indirect effects on bone metabolism, and the reduced levels of these hormones resulting from hormone ablation therapy in patients with breast and prostate cancer may lead to loss of bone mass and an increased risk of osteoporotic fractures. Men receiving androgen deprivation therapy for prostate cancer may also undergo loss of muscle mass, with resulting indirect effects on bone [49].

The aim of this review is to provide a historical perspective on the medical management and consequences of bone metastases and CTIBL, using the available data to encourage best practice and to highlight the benefits of early and sustained treatment.

History of the management of bone metastasis complications

Management of the consequences of bone metastases with bisphosphonates began in the 1980s with the development of the first-generation intravenous bisphosphonate clodronate, which was licensed in Europe in 1992 for management of osteolytic lesions, hypercalcaemia and bone pain associated with skeletal metastases in patients with carcinoma of the breast or multiple myeloma (Supplementary Table 1). This was followed by the second- and third-generation agents, most notably zoledronic acid (ZA), which was first approved in 2001. Bisphosphonates are chemically stable analogues of pyrophosphate compounds such as inorganic pyrophosphate, which are found widely in nature [51]. The high affinity of bisphosphonates for calcium ions means that they attach to hydroxyapatite binding sites on the bone surface, especially in locations undergoing active resorption. The bisphosphonate molecule is then internalised by osteoclasts during resorption, leading to inhibition of osteoclast function [6]. With first-generation, non-nitrogen-containing bisphosphonates, this process occurs via the disruption of cellular metabolism, leading ultimately to apoptosis [1].

The second- and third-generation bisphosphonates differ from first-generation agents because they have a nitrogen-containing side group. These agents can be divided into alkyl-amino bisphosphonates (the second-generation agents pamidronate, alendronate, risedronate, and the third-generation agent ibandronate) and heterocyclic bisphosphonates (the third-generation agent ZA; see below). The nitrogen-containing bisphosphonates are generally more potent than first-generation agents as, in addition to hydroxyapatite binding, they impair intracellular signalling in osteoclasts by inhibiting the enzyme farnesyl diphosphate synthase [1,51]. The third-generation bisphosphonates differ from second-generation agents in that the nitrogen group is contained in the R2 side-chain, leading to more potent inhibition of farnesyl synthase, a key enzyme in metabolic pathways involved in osteoclast morphology and function [52].

In 2010, the first, and to date only, RANKL-targeted monoclonal antibody, denosumab, was also licensed for management of the consequences of bone metastases from solid tumours. Management of bone metastases is generally evaluated in terms of the prevention of SREs, using parameters such as time to first SRE, skeletal morbidity rate or multiple-event analysis [12,53]. Other endpoints used to evaluate efficacy relevant from the patient's perspective include bone pain (evaluated as an adverse event or using instruments such as the Bone Pain Index), and survival.

First-generation bisphosphonates

Bisphosphonates were first used successfully in patients with cancer

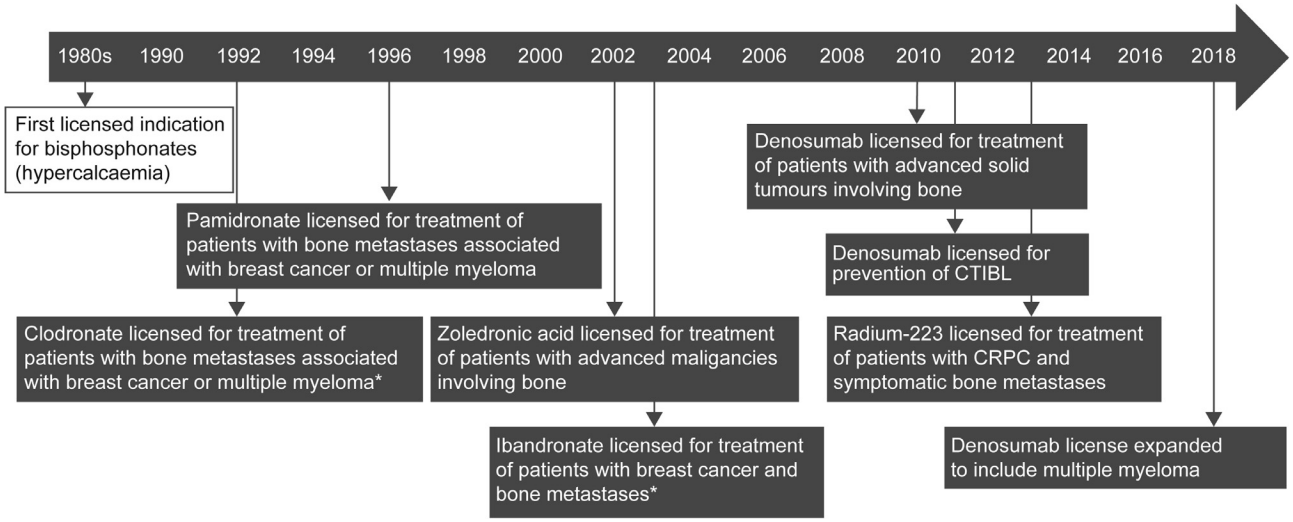

Fig. 1. Timeline of key events in the development of bisphosphonates and denosumab in the management of bone health in patients with advanced malignancies. * Not licensed in the USA. CRPC = castrate-resistant prostate cancer; CTIBL = cancer therapy-induced bone loss.

Table 1
Key results from studies of bisphosphonates and denosumab in patients with solid tumours and bone metastases.

Study	Year	Duration	Treatment	SRE, %	Time to first SRE, days	SMR, events per year
Breast cancer						
Hortobagyi et al. [28]	1996	12 cycles	Pamidronate	43*	399*†	–
			Placebo	56	213†	
Theriault et al. [29]	1999	24 cycles	Pamidronate	56*	317*†	2.4*
			Placebo	67	210†	3.8
Rosen et al. [30]†	2001	13 months	ZA	44	373	1.13
			Pamidronate	46	363	1.40
Berenson et al. [32]	2001	10 months	ZA	33	231	–
			Pamidronate	30	254	
Rosen et al. [31]‡	2003	25 months	ZA	47	376	1.04
			Pamidronate	51	356	1.33
Body et al. [39]	2003	96 weeks	IV ibandronate	51*	354*	–
			Placebo	62	232	
Rosen et al. [33]	2004	12 months	ZA	43	310*	0.98
			Pamidronate	45	174	1.55
Body et al. [40]	2004	96 weeks	Oral ibandronate	45	632	–
			Placebo	52	454	
Stopeck [41]	2010	34 months#	Denosumab	–	NR	0.45
			ZA		804†	0.58
Barrett-Lee et al. [34]	2014	96 weeks	ZA	41	693	0.44
			Oral ibandronate	42	679	0.50
Castrate-resistant prostate cancer						
Saad et al. [35]	2002	15 months	ZA	33*	NR*	0.80
			Placebo	44	321	1.49*
Saad et al. [36]	2004	24 months	ZA	38*	488*	0.77*
			Placebo	49	321	1.47
Fizazi et al. [42]	2011	11–12 months#	Denosumab	36	630*†	–
			ZA	41	520†	
Solid tumours						
Rosen et al. [37]	2003	9 months	ZA	38	230*	2.24
			Placebo	44	163	2.52
Rosen et al. [38]	2004	21 months	ZA	39	236*	1.74*
			Placebo	46	155	2.71
Henry et al. [43]‡	2011	7 months#	Denosumab	–	627†	–
			ZA		496†	
Henry et al. [44]	2014	6–7 months#	Denosumab	–	651*†	–
			ZA		469†	

Abbreviations: IV = intravenous; NR = not reached; SMR = skeletal morbidity rate; SRE = skeletal-related event; ZA = zoledronic acid.
* $p < 0.05$ vs comparator.
† Converted from months using the formula Days = Months × 30.4375.
‡ Also includes patients with multiple myeloma.
# Median duration.

for the treatment of hypercalcaemia in the early 1980s, many years before data from large randomised, controlled trials showed they could prevent SREs [51]. Hypercalcaemia of malignancy was the setting used to derive active bisphosphonate doses for the treatment of bone metastases. Small placebo-controlled studies of clodronate in women with breast cancer metastatic to the bone began in the 1980s [54]. These studies showed benefit in terms of bone pain, extension of bone metastases into soft tissue and formation of new osteolytic foci, but approval by regulatory agencies did not occur until these data were confirmed in larger randomised controlled trials [24]. In metastatic castration-resistant prostate cancer (CRPC), the efficacy of clodronate is limited, with no beneficial effect on SREs (Table 1) [25–27], and treatment is not licensed in these patients.

Second-generation bisphosphonates

The clinical activity of nitrogen-containing bisphosphonates was first demonstrated in studies of pamidronate by a number of European groups in the early 1990s [55–57]. The first randomised, placebo-controlled trials were conducted in the USA in the mid-to-late 1990s, and results showed that pamidronate reduced skeletal morbidity by ~33%, increased median time to SRE by ~50%, and reduced the proportion of patients who experienced SREs by ~20% [28,29]. It is important to note, however, that the therapeutic anticancer landscape has changed considerably over the past 20 years, and so these values must be interpreted in context and may no longer be valid with respect to current standard of care.

By the late 1990s, the potential of bisphosphonates in the treatment of patients with bone metastases had been confirmed [58–60]. In 1996, pamidronate was approved for the treatment of complications arising from osteolytic metastases in breast cancer, and soon became the treatment of choice [30,61]. While other second-generation bisphosphonates, including alendronate, are available for the treatment of osteoporosis, they are not licensed for the management of bone metastasis complications.

Bisphosphonate treatment is generally well tolerated, the main side effects being acute-phase reactions (e.g. chills, fever, bone pain and fatigue) and changes in serum ion levels, particularly calcium, magnesium and phosphorus [62]. Bisphosphonates are also associated with a dose- and infusion-rate-dependent impact on renal function, and renal function should be monitored during treatment [62]. In some patients receiving long-term bisphosphonate therapy, particularly with nitrogen-containing bisphosphonates, osteonecrosis of the jaw (ONJ) has been reported as a result of effects on osteoclast-mediated bone resorption and osteoclast formation [63].

Third-generation bisphosphonates

The third-generation bisphosphonate ZA differs from other bisphosphonates in that the nitrogen-containing R2 side-chain is a heterocyclic ring [64]. In addition to having increased potency on bone, ZA is also administered in a 15-min infusion, compared with 2 h for pamidronate. Furthermore, data suggest that ZA has anti-neoplastic effects resulting from decreased dissemination of tumour cells in bone marrow, inhibition of tumour cell adhesion, invasion, and proliferation, induction of apoptosis and inhibition of angiogenesis [64–68]. The clinical relevance of these effects has not been established.

In 1999, the first data demonstrating the clinical activity of ZA (in patients with cancer-related hypercalcaemia) were published [69]. Subsequently, several placebo-controlled and head-to-head studies of ZA versus other bisphosphonates were conducted in patients with metastatic breast cancer [30–34] and CRPC [35,36]. ZA was found to be more effective than pamidronate for reducing the incidence of SREs (primary endpoint in most studies), although this difference was not statistically significant in all studies (Table 1). One study in breast cancer also demonstrated a significant increase in time to first SRE (secondary endpoint) with ZA versus pamidronate [33]. The incidence of bone pain was similar with these agents [30,31,33].

ZA is the only bisphosphonate shown to significantly reduce skeletal complications from bone metastases in men with advanced prostate cancer [12], but the benefits of ZA are less clear in men with hormone-sensitive prostate cancer (HSPC) and bone metastases. Data from a randomised, controlled trial showed no difference in overall survival between ZA and placebo, and only a small numerical benefit for ZA in terms of the time to first SRE [70]. Information about the efficacy of ZA in other solid tumours is sparse. Most data come from a single randomised, double-blind, placebo-controlled trial in patients with mixed solid tumours, including lung cancer [37]. Overall, ZA was associated with a slight reduction in the incidence of SREs (primary endpoint) after 9 months versus placebo, a significantly prolonged time to first SRE and a reduced annual incidence of SREs. In the longer term (21 months), ZA significantly reduced the percentage of patients who experienced SREs and prolonged the time to first SRE compared with placebo (Table 1) [38]. Furthermore, in a retrospective analysis of data from the study, ZA was associated with reduced mortality versus placebo in the subset of patients who had elevated levels of the bone turnover marker N-telopeptide of type I collagen [71]. This positive effect on survival in patients with poor prognostic features, including elevated levels of bone markers, was confirmed in a subsequent exploratory analysis of three randomised controlled trials of ZA in patients with solid tumours [72]. ZA has also been the treatment of choice for myeloma-related bone disease [73], further discussion of which is outside the scope of the current paper.

Nephrotoxicity is one of the most clinically significant adverse events associated with ZA. It can limit ZA use in patients receiving chemotherapy agents such as cisplatin, particularly in patients who are older, with comorbidities and, in the case of lung cancer, a history of tobacco use [53]. Other notable side effects with ZA are similar to those of the first- and second-generation bisphosphonates, including acute-phase reactions, hypocalcaemia, and ONJ [53]. In an attempt to reduce the increased risk of ONJ resulting from accumulation of ZA in bone with prolonged administration, extended dosing intervals (every 12 weeks vs the standard dosing interval of 4 weeks) have been investigated [74–76]. Results to date suggest that dosing every 12 weeks is non-inferior to dosing every 4 weeks in terms of prevention of SREs; this may be related to the preferential binding, potency and accumulation of ZA in bone, prolonging its pharmacologic activity. The incidence of ONJ was similar or lower with dosing every 12 weeks compared with dosing every 4 weeks [74–76]. In the largest study, however, significantly more patients receiving ZA every 12 weeks required bone surgery within 2 years of enrolment (secondary endpoint) compared with 4-weekly ZA (4.8% vs 2.5%, respectively) [76]. It should be noted, however, that this was an open-label non-inferiority study in which a high percentage of patients (40%) withdrew before experiencing an SRE, and there was no assessment of survival. Thus, overall data from studies of extended-interval ZA dosing to date support the use of 12-weekly treatment. It is not clear, however, whether there are subgroups, such as those with aggressive bone disease, who would benefit more from 4-weekly treatment or in whom 12-weekly treatment should be introduced after a period (e.g. 1 year) of monthly treatment.

Ibandronate is a third-generation bisphosphonate approved in Europe since 2003 as oral and intravenous formulations for prevention of SREs in patients with breast cancer. In randomised, placebo-controlled trials, oral and intravenous ibandronate were both found to reduce the incidence of new bone events by 38% [39,40]. While ibandronate has been shown to have similar effects on serum cross-linked C-terminal telopeptide of type I collagen (CTX), urinary CTX, bone alkaline phosphatase, amino-terminal procollagen propeptide of type I collagen, and osteocalcin as ZA in a Phase III study [77], a second Phase III study showed that oral ibandronate was inferior to ZA in terms of preventing SREs [34]. Oral ibandronate may, however, be an alternative agent for patients who have a strong preference for oral treatment or in whom convenience of treatment is an important factor [34,78]. The third-generation bisphosphonate risedronate is licensed for the treatment of osteoporosis in Europe and the USA, and Paget's disease in the USA, but has not been approved for the management of complications arising from bone metastases.

Overall, data show that ZA is the most active bisphosphonate in terms of preventing morbidity from bone metastases in patients with breast cancer, CRPC, lung and other solid tumours [53,79]. From its first approval in 2002 [80], ZA became standard of care for the prevention of skeletal complications in patients with bone metastases from solid tumours for more than a decade [81]. In the mid-2000s, it was noted, however, that SREs still occurred in patients receiving ZA and metastases continue to progress in the skeleton [82].

RANKL-targeted monoclonal antibodies: Denosumab

One of the key regulatory factors in bone remodelling is RANKL [83]. RANKL mediates osteoclast formation, function and survival, and is an important therapeutic target in the management of bone metastases [84], as the receptor RANK is expressed in a range of tumour types, including breast and lung cancers [81,85–88]. Denosumab is a human monoclonal IgG2 antibody that acts by binding with high affinity to membrane-bound and soluble forms of RANKL, decreasing osteoclast formation and activity [1,83,84]. Denosumab may also have effects on tumour cells independent of its role in bone homeostasis [81,89]. For example, the pro-tumourigenic effects of progesterone are mediated largely via RANKL [87,90–92], while RANK signalling induces stem-cell characteristics in human and mouse mammary epithelial cells, increasing recurrence and metastasis [88,93,94]. These effects have been observed primarily in preclinical studies, and their clinical relevance is unknown, although a similar effect of RANKL as a mediator of progesterone has also been observed in female mammary epithelia from patients undergoing mammoplasties and in carriers of the *BRCA1* gene [91,95]. This suggests a possible role for RANKL inhibitors in the prevention of breast cancer in women at high risk.

Data from an early study utilising single denosumab doses of 0.1, 0.3, 1.0, or 3.0 mg/kg demonstrated rapid suppression of bone turnover in patients with bone metastases, as well as greater reductions in bone turnover markers than with a single 90 mg dose of pamidronate [96]. Numerous head-to-head studies of denosumab (120 mg every 4 weeks) versus ZA (4 mg every 4 weeks) have been conducted in patients with different tumour types, including breast cancer [41], prostate cancer [42] and other solid tumours [43–45]. These pivotal studies were non-inferiority trials, designed to allow superiority testing according to the Hochberg method as a secondary endpoint and acknowledged by the US Food and Drug Administration. In addition, pooled analyses have been

Table 2
Key results from an integrated analysis of three head-to-head studies (n = 5723) comparing denosumab and zoledronic acid [99].

Parameter	Hazard ratio (95% CI)*	*P*-value
Time to first SRE (primary endpoint)	0.83 (0.76–0.90)	< 0.001
Time to multiple SREs	0.83 (0.76–0.90)	< 0.001
Pain worsening	0.92 (0.86–0.99)	0.026
Overall survival	0.98 (0.91–1.06)	0.617
Disease progression	1.02 (0.96–1.09)	0.697

Abbreviations: CI = confidence interval; SRE = skeletal-related event.
* Values < 1 favour denosumab.

conducted of three studies in breast cancer, prostate cancer, other solid tumours and multiple myeloma (for which denosumab was recently licensed; Fig. 1) [97,98]. In an integrated analysis of head-to-head studies (n = 5723), denosumab significantly delayed the time to first SRE compared with ZA in patients with solid tumours and bone metastases (Table 2) [99]. Denosumab also delayed time to multiple SREs and pain worsening, while the drugs had a similar effect on overall survival and disease progression (Table 2). In the lung cancer subgroup of a study in patients with solid tumours, however, denosumab was associated with improved overall survival compared with ZA [45]. To date there are no Phase III data to demonstrate that denosumab treatment can prevent SREs in patients with metastatic HSPC [49], although such tumours are covered by the product label [20,21].

Unlike many bisphosphonates, which are administered intravenously, denosumab is given subcutaneously as a single 120-mg injection every 4 weeks, improving the convenience and acceptability of treatment for patients [49,53,100], as well as the time required from healthcare professionals to deliver the medication [101]. The safety profile of denosumab is broadly similar to that of ZA, with both drugs associated with a low incidence of hypocalcaemia and ONJ. However, the incidences of hypocalcaemia and serious hypocalcaemia are higher with denosumab [102], as potent inhibition of osteoclast function reduces the amount of skeletal calcium released into the circulation, while the incidence of renal toxicity is higher with ZA [53]. Recent data show that the incidence of hypocalcaemia in patients receiving denosumab can be as high as 30% despite mandatory Vitamin D and calcium substitution, although Grade 3 + hypocalcaemia was rare (1.3%) [103]. Unlike ZA, however, denosumab is not cleared by the kidneys [104]. The incidence of hypocalcaemia is increased in patients with severe renal impairment receiving denosumab compared with patients with milder or no renal impairment. Other risk factors for hypocalcaemia include prostate cancer or small-cell lung cancer, reduced creatinine clearance, and higher baseline levels of the bone turnover markers urinary N-telopeptide of type I collagen and bone-specific alkaline phosphatase [105]. Recent data have shown, however, that the appearance of hypocalcaemia is very rare after 12 months of treatment [103].

Overall, denosumab has benefits over ZA in metastatic solid tumours because of its superior efficacy in terms of delaying the time to SREs, the convenience of a subcutaneous injection and the lack of requirement for renal monitoring [53,79]. These aspects are also important to patients in determining their preference for one treatment over another. When 484 European patients were asked what aspects of treatment were most important to them, delaying the time until first SRE and worsening pain, and a low risk of renal complications, were considered most important [100]. No significant difference in ONJ rates between denosumab and ZA has been reported in randomised controlled clinical trials [53,79]. However, in a registry study of ONJ in 327 adults with a diagnosis of any cancer and ONJ, 97% had previously received either bisphosphonates (56%), denosumab (18%), or both (21%) [106]. Whichever agent is prescribed, the risks of ONJ must be discussed with patients before beginning denosumab or bisphosphonate treatment. Dentists have a key role to play as part of the multidisciplinary team in preventing and managing ONJ [107]. Maintaining dental hygiene, avoiding bone trauma, and preventing and treating dental infections before and during therapy are essential to minimise the risk of ONJ [108]. Furthermore, any necessary dental surgery should be completed before initiating therapy. If invasive dental surgery is required while patients are receiving bisphosphonate or denosumab therapy, it is recommended that treatment is withheld for 2 months after surgery, although there is little evidence in this area [108].

The potential health economic benefits of treatment must also be taken into account, as studies have shown that patients with solid tumours who experience ≥ 1 SRE incur additional healthcare-related costs [109,110]. Treatments that reduce the incidence of SREs, therefore, have the potential to reduce the cost burden to healthcare services and society. While the acquisition cost of the monoclonal antibody denosumab is higher than that of generic bisphosphonates, cost-effectiveness analysis has shown that incremental costs per quality-adjusted life year (QALY) and per SRE avoided with denosumab are well below willingness-to-pay thresholds, and thus denosumab can be considered cost effective for prevention of SREs [111,112]. In an alternative cost-effectiveness analysis conducted based on US data, denosumab and ZA were associated with similar QALYs gained, and thus the authors concluded that the lower cost of ZA made it the optimal treatment [113]. Other authors have, however, described significant methodological flaws in the analysis, including failing to account for the superiority of denosumab over ZA in terms of SRE reduction, underestimating the prevalence of SREs and their cost burden, and limiting the time horizon of the analysis to 2 years [114].

Bisphosphonates and denosumab for the prevention of CTIBL

In addition to their role in reducing the risk of SREs in patients with bone metastases, benefits were also reported for several nitrogen-containing bisphosphonates in preventing CTIBL in patients with breast and prostate cancer. Observed benefits include improved bone mineral density (BMD) with risedronate (lumbar spine, +2.2% vs –1.8% with placebo; hip, +1.8% vs –1.1% with placebo; both $P < .0001$) [115] and ibandronate (lumbar spine, +3.0% vs –3.2% with placebo; hip, +0.6% vs –3.9% with placebo; both $P < .001$) [116] in women with breast cancer receiving hormonal therapy. Furthermore, alendronate, risedronate and pamidronate prevented BMD loss in men with locally advanced prostate cancer [117]. Similarly, several ZA studies confirmed the benefits of treatment (4 mg every 6 months) for reducing aromatase inhibitor-related bone loss in women with breast cancer [118–122]. Findings showed that adverse events with bisphosphonate therapy were mild and could be either prevented with suitable measures or easily managed [68].

Compared with breast cancer, data relating to the use of ZA for the prevention of CTIBL in patients with prostate cancer receiving androgen-deprivation therapy are limited. The available data suggest that ZA can improve BMD during androgen-deprivation therapy [123], although it is not clear whether this translates to improved fracture rates, and treatment is not associated with prolonged survival [124].

Denosumab has also been evaluated for the prevention of CTIBL in patients with breast cancer [125,126], HSPC [127] and CRPC [128,129]. For example, in the Austrian Breast & Colorectal Cancer Study Group-18 study, 3420 postmenopausal patients with early hormone receptor-positive breast cancer receiving treatment with aromatase inhibitors were randomised to denosumab 60 mg every 6 months or placebo [126]. The results of the primary analysis showed a significant reduction in the time to first fracture in women receiving denosumab compared with placebo, independently of baseline BMD (HR: 0.50; 95% CI: 0.39–0.65; $P < .0001$). Denosumab (as Prolia®, Amgen, Thousand Oaks, CA, USA) was licensed in 2011 for treatment of osteoporosis in postmenopausal women and for men at an increased risk of fractures, including as a result of CTIBL, as well as for the

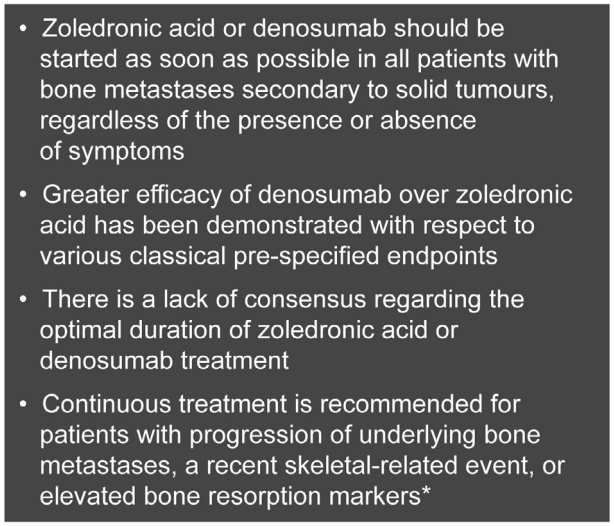

Fig. 2. Key points from the 2014 European Society for Medical Oncology clinical practice guidelines [12]. * While the use of markers in decision making is controversial [133], there are biochemical studies supporting a therapy switch when bone markers remain elevated [134].

treatment of bone loss associated with hormone ablation in patients with breast or prostate cancer at increased risk of fractures [130]. It is important to note that discontinuation of denosumab in postmenopausal women with reduced BMD is associated with an increase in multiple vertebral fractures to the level observed in untreated participants [131]. Therefore, patients with osteoporosis who discontinue denosumab should transition to an alternative antiresorptive treatment. This transition should be not carried out until 7–8 months after the last denosumab injection, to ensure maintenance of BMD gains [132]. Furthermore, in women with breast cancer receiving aromatase inhibitors, the increase in fracture risk after discontinuing denosumab was negated in women who also discontinued their aromatase inhibitor therapy before, or within 6 months after, stopping denosumab [133]. These findings warrant further research to fully evaluate the risk of fracture in patients with cancer who discontinue denosumab.

Treatment guidelines and real-world treatment patterns

In 2014, the European Society for Medical Oncology (ESMO) published clinical practice guidelines on bone health in patients with cancer [12] (key points are summarised in Fig. 2 [134,135]). Treatment with ZA or denosumab was recommended in patients with bone metastases from either breast cancer or prostate cancer, irrespective of the presence or absence of symptoms. These agents were also recommended in patients with advanced lung cancer, renal cancer and other solid tumours with bone metastases, particularly those at high risk of SREs and a life expectancy of > 3 months [12]. The ESMO guidelines state that bisphosphonates or denosumab should be started as soon as metastatic bone disease is diagnosed and continued throughout the course of the disease [12], although this recommendation may not be followed in routine practice [136]. The ESMO guidelines are currently under revision and a new version is scheduled to be published in 2019.

In 2017, the American Society for Clinical Oncology (ASCO) and Cancer Care Ontario (CCO) published guidelines on bone modifying agents in metastatic breast cancer [137]. Like ESMO, they recommend treatment for all patients with evidence of metastases, although the ASCO-CCO guidelines include pamidronate as a recommended agent in addition to denosumab and ZA. They further note that patients with bone pain should receive analgesia in addition to denosumab or a bisphosphonate. Neither the ESMO nor ASCO-CCO guidelines address the issue of whether bisphosphonate or denosumab treatment could be safely withdrawn in patients with a very small number of asymptomatic bone metastases, as life expectancy in these patients can be high [138] and treatment can place them at risk of ONJ and pathological femur fractures. Delaying treatment in these 'low risk' patients has not, however, been evaluated in controlled trials, and there are currently no predictive tools to assess the risk of such patients developing SREs.

In 2016, a consensus panel concluded that bisphosphonates for prevention of CTIBL should be part of routine clinical practice in all patients with either a bone density T-score of < –2.0 or two or more clinical fracture risk factors [139]. The authors noted, however, that bisphosphonates are not licensed for either indication.

The use of bisphosphonates and denosumab in clinical practice has been evaluated in several real-world data sets. Data from a German treatment registry showed that most patients (89%) with bone metastases from breast cancer receive treatment in line with guidelines, with bisphosphonates (primarily ZA) or denosumab started a median of 3 weeks after diagnosis of bone metastases [140]. Notably, data from the Adelphi Prostate Cancer and Breast Cancer Disease Specific Programmes showed that patients with breast cancer are more likely to receive bisphosphonate or denosumab treatment than those with prostate cancer [141]. (Body JJ et al. manuscript submitted). Overall, 11% of patients with breast cancer and 26% of those with prostate cancer did not receive any treatment with bisphosphonates or denosumab. Furthermore, in an analysis of 47,052 patients with solid tumours and bone metastases who had a minimum of 6 months of continuous enrolment in a health plan in the USA, 28,135 patients (60%) did not receive denosumab or an intravenous bisphosphonate within 6 months of their diagnosis of bone metastasis [142]. Thus it is clear that, while many patients in real-world clinical practice receive guideline-recommended treatment, there may be substantial differences between countries.

The future

Despite the advances made in the management of bone health in patients with cancer, there are still several off-label areas in which further research is needed (Fig. 3). As noted earlier, the optimal duration of therapy remains unclear [12,79,143]. Extended dosing intervals or intermittent therapy may be used in practice, and the published data comparing different ZA dosing schedules are described above [74–76]. Studies investigating 4-weekly vs 12-weekly administration of denosumab are also underway (ClinicalTrials.gov: NCT02721433; NCT02051218 [103]). Additional areas in which research is needed include strategies to optimise the risk–benefit ratio of treatment with bisphosphonates and denosumab, and their use in patients with very severe disease.

In recent years, developments in imaging and molecular analysis have allowed greater characterisation of the microenvironment within bone that allows metastases to develop (the 'metastatic niche') [144]. This microenvironment is actively modified by the primary tumour before metastasis occurs [145]. When tumour cells first colonise bone, they enter a dormant state before subsequently being reactivated by mechanisms including osteoclast-mediated modelling of the endosteal bone surface. This process represents a potential target for future therapeutic intervention, as well as a means of improving risk stratification [144,146]. The precise mechanisms that underly dormancy and reactivation, however, remain to be discovered, and may vary between cancer types [147].

There are limited data on efficacy and safety of bisphosphonates and denosumab in patients with bone metastases arising from other solid tumours such as melanoma, renal cell carcinoma and colon cancer. In these patients, and in those with lung cancer, use of targeted therapy and immunotherapy has led to an increase in life expectancy [148–151]. Data so far suggest that denosumab may have the potential to enhance the effects of immunotherapy without increasing adverse

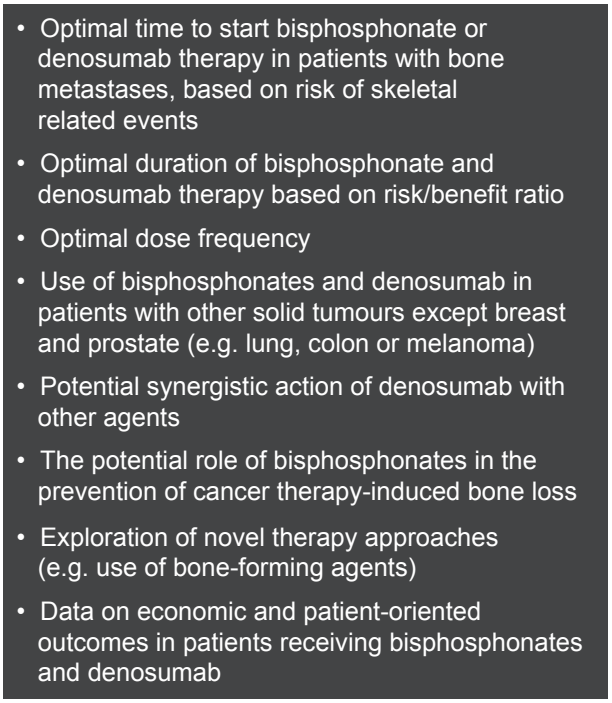

Fig. 3. Areas where further research is needed with regard to management of bone health in patients with solid tumours.

event burden, including in non-small-lung cancer [152–155]. Moreover, the combination of denosumab with immunotherapy is in clinical use in patients with non-small-lung cancer and bone metastases (RvM, personal communication), and is also being evaluated in ongoing trials such as DENIVOS (ClinicalTrials.gov: NCT03669523). Denosumab may also have additive actions with novel biologic agents such as: crizotinib or other ALK inhibitors; erlotinib; gefitinib; afatinib; CTLA4, PD-1 and PD-L1 inhibitors; and c-Met inhibitors [81,156,157]. Trials involving PD-1 and PD-L1 inhibitors in combination with denosumab in patients with solid tumours are underway, such as the DENIVOS study mentioned above, as well as the KEYPAD study in clear cell renal carcinoma (ClinicalTrials.gov: NCT03280667) and the CHARLI study in melanoma (ClinicalTrials.gov: NCT03161756).

Radium-223 is used for the management of bone metastases in men with CRPC and no known visceral metastases (Supplementary Table 1), and data show that it can delay SREs and improve overall survival [158]. Notably, sub-analysis of the pivotal ALSYMPCA trial showed that concomitant bisphosphonate use was a significant predictor for reduced risk of SRE in men with CRPC receiving radium-223 [48]. Data from an open-label, uncontrolled, early access programme suggested that survival benefits were significantly greater when radium-223 was combined with enzalutamide and/or abiraterone, or with denosumab, compared with radium-223 alone [159]. Recently presented data from the ERA-223 study, however, suggest that combination of radium-223 with abiraterone plus prednisone/prednisolone did not improve either symptomatic SRE-free survival or overall survival, and was associated with an increased risk of fractures [160]. The fracture rate was, however, lower in men who were also receiving denosumab or a bisphosphonate. As a result, only those participants who were receiving denosumab or a bisphosphonate, regardless of allocated treatment arm, were allowed to continue the study (patients who started the study without receiving denosumab or a bisphosphonate were not allowed to start one after randomization). Although this bone-protective effect was not prospectively evaluated, these data suggest that bisphosphonates and denosumab are important therapeutic tools irrespective of the specific anti-cancer treatment used.

Although there are many novel agents under development for advanced cancer that may also have wider effects on bone, there are few trials in progress evaluating new therapies that specifically target the bone microenvironment. More research is also needed into the use of bone-forming (anabolic) agents in patients with bone metastases, as there are currently no drugs licensed for use in solid tumours that increase bone formation. In most cancers, including breast cancer and multiple myeloma, though not prostate cancer, bone formation is reduced and lytic bone metastases often predominate [161,162]. Given that denosumab is a highly potent anti-resporptive agent, the need for new anabolic agents is greater than that for novel anti-resorptives. Bone anabolic agents with potential for treatment of patients with bone metastases include everolimus, proteasome inhibitors, sotatercept, and anti-WNT, DKK1, and sclerostin antibodies such as romosozumab [163], although data on these new agents are currently lacking.

Summary and conclusions

Patients with solid tumours are at risk of bone metastases, which have a severe impact on morbidity and mortality, and also lead to substantial increases in healthcare resource utilisation and costs. Nonetheless, many patients with solid tumours and bone metastases are not currently protected from bone complications. Bisphosphonates and denosumab have an important role in the management of bone health in patients with solid tumours, in terms of reducing the frequency of complications associated with existing bone metastases and, in the case of denosumab, in the management of CTIBL. In patients with bone metastases, ZA and denosumab have been shown to reduce the incidence of SREs. Treatment also delays the onset of bone pain in patients for whom bone metastasis is the most common cause of pain, and early initiation of treatment is important to maximise both efficacy and pain control. Superiority of denosumab over ZA has been demonstrated in an integrated analysis of solid tumour trials for prevention of SREs, reduction in bone pain and improvement of quality of life, with associated benefits for patients, healthcare systems and society. In patients with breast cancer receiving hormonal therapy, ZA and denosumab can prevent bone loss and maintain BMD, and denosumab can also prevent CTIBL in breast and prostate cancer. Denosumab, but not ZA, is licensed for these indications. Areas in which further research is necessary include length of therapy, management of side effects, particularly in the long term, and the potential differences in risk of SREs over time in different tumour types.

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Author contributions

All authors were involved in the drafting and review of the manuscript and approved the final version for submission.

Appendix A. Supplementary material

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