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REVIEW ARTICLE

Hypercalcaemia and hypocalcaemia: finding the balance

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Abstract
Calcium metabolism in cancer and hypercalcaemia of malignancy The balance between bone formation and resorption may be disrupted in patients with cancer, leading either to increased bone resorption, calcium release, and possibly hypercalcaemia, or to increased bone formation, sequestration of calcium, and possibly hypocalcaemia. In adults, hypercalcaemia of malignancy is most common in patients with tumours that produce factors that induce osteoclast activation and enhance bone resorption. Impaired renal function and increased renal tubular calcium resorption may further affect calcium levels.

Treatment of hypercalcaemia of malignancy Inhibitors of bone resorption, first the bisphosphonates and, later, denosumab, have been shown to be effective in hypercalcaemia treatment. Bisphosphonates (which are administered intravenously) are approved for hypercalcaemia of malignancy and are the current mainstay of treatment, whereas denosumab (which is administered subcutaneously) may offer an option for patients who do not respond to bisphosphonates or suffer from renal insufficiency.
Hypocalcaemia: treatment and prevention Hypocalcaemia is most common in patients with prostate cancer and osteoblastic bone metastases, but can occur in patients with a variety of tumour types who are receiving inhibitors of bone resorption. While patients often respond to calcium and vitamin D supplementation, prevention should be the aim; at-risk patients should be identified before starting treatment with inhibitors of bone resorption, be closely monitored during at least the first few months of treatment, and receive concomitant calcium and vitamin D supplementation unless hypercalcaemia is present.
Conclusion Both hypercalcaemia and hypocalcaemia can be serious if left untreated. It is therefore important that patients with cancer are closely monitored and receive adequate prevention and treatment measures to maintain normal blood calcium levels.

Highlights
- Disruption of bone turnover in cancer can lead to hypercalcaemia or hypocalcaemia
- Both conditions can be serious if left untreated
- Agents that inhibit bone resorption are effective treatments for hypercalcaemia
- Bone resorption inhibitors can cause or aggravate hypocalcaemia
- Physicians need to monitor calcium levels when treating patients with cancer

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Keywords Hypercalcaemia · Hypocalcaemia · Hypercalcaemia of malignancy · Denosumab · Bisphosphonates

Introduction

Several organs contribute to the maintenance of healthy blood calcium levels, including the kidneys, parathyroid glands,

intestines, and bone. The bone is a dynamic tissue that is constantly being remodelled by specialised bone-forming cells, osteoblasts, and bone-resorbing cells, osteoclasts [1], and acts as a major calcium sink [1, 2]. The normal balance of bone metabolism is often uncoupled in patients with advanced cancer, particularly in those with metastatic bone lesions. This can lead to hypercalcaemia of malignancy or hypocalcaemia, both of which can have serious consequences.

In order to maintain blood calcium homeostasis in patients with cancer, it is important to understand the underlying mechanisms of hypercalcaemia and hypocalcaemia in the context of the management of metastatic bone disease.

Calcium metabolism in cancer

The balance of bone formation and resorption can be disrupted in patients with cancer by systemic factors released from the primary tumour and by local effectors released from tumour cells that have metastasised to bone (Fig. 1) [1].

In osteoblastic metastases, tumour cells produce osteoblast-stimulating factors, such as endothelin-1, platelet-derived growth factor, fibroblast growth factor, and bone morphogenetic proteins, proteases (e.g. matrix metalloproteinases, prostate-specific antigen, urokinase-type plasminogen activator), all of which promote osteoblast proliferation and bone formation (Fig. 1) [4–7]. Osteoblastic metastases are common in patients with prostate cancer [8, 9]; endothelin-1 has been shown to be increased in the blood of such patients [6]. Calcium is sequestered from the blood during the development of osteoblastic metastases [10]; therefore, patients with prostate cancer and osteoblastic metastases are most at risk of developing hypocalcaemia.

In osteolytic metastases, tumour cells release factors that ultimately activate osteoclasts (Fig. 1). In breast cancer, the most important of these factors is parathyroid hormone-related protein (PTHrP) [11–13]. Other examples include transforming growth factor beta [14], interleukin-1 and interleukin-6, and tumour necrosis factor alpha [15]. These factors stimulate bone marrow stromal and osteoblast cells to express RANK ligand (RANKL), which signals via its cognate receptor RANK, expressed on osteoclast precursor cells and activated osteoclasts [16]. Signalling through the RANK receptor induces osteoclast maturation and bone resorption [17–19]. During bone resorption, calcium is released causing a rise in blood calcium concentration [2]. Additionally, growth factors stored in the bone matrix are released and stimulate tumour cell proliferation and further release of PTHrP, feeding into the vicious cycle of bone metastases and tumour growth [20]. Tumours of the breast and lung, and multiple myeloma, predominantly cause osteolytic metastases and lytic bone lesions, respectively [21–23]; patients with these malignancies are, therefore, most at risk of developing hypercalcaemia of malignancy.

Although there are clear distinctions in the causes and epidemiology of osteolytic and osteoblastic bone metastases, it should be noted that these two types of bone lesion represent extremes of a spectrum of metastatic bone disease [24]; a substantial proportion of patients have bone metastases with both osteolytic and osteoblastic elements. For example, in one study, the majority of patients with castration-resistant prostate cancer, a spectrum of bone lesions from osteolytic to osteoblastic was present [25].

Calcium homeostasis can also be disrupted in patients with advanced cancer that has not metastasised to bone. In these patients, tumour-derived systemic factors (predominantly PTHrP) increase blood calcium concentrations by enhancing osteoclast activation and bone resorption and by increasing renal tubular calcium reabsorption [26].

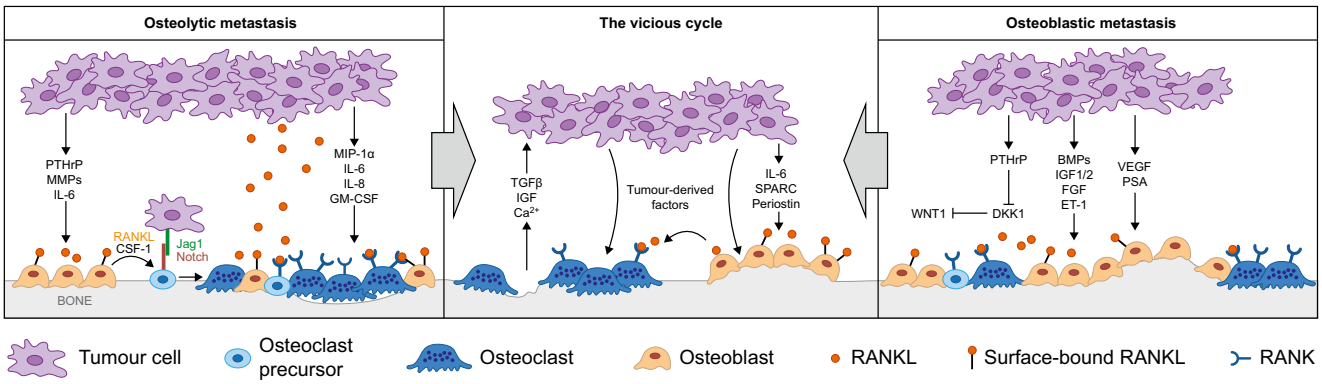

Fig. 1 Mechanisms underlying osteolytic and osteoblastic metastasis. Adapted from Cell, Vol: 151, Ell B. and Kang Y. Snapshot: bone metastasis, Pages: 690–90. Copyright (2015), with permission from Elsevier [3]. *BMP* bone morphogenetic protein, *CSF-1* colony-stimulating factor 1, *DKK1* Dickkopf Wnt signalling pathway inhibitor 1, *ET-1* endothelin 1, *FGF* fibroblast growth factor, *GM-CSF* granulocyte-macrophage colony-stimulating factor, *IGF* insulin-like growth factor, *IGF 1/2* insulin-like growth factor 1/2, *IL-6* interleukin 6, *IL-8* interleukin 8, *MIP-1a* macrophage inflammatory protein 1 alpha, *MMP* matrix metalloproteinase, *PSA* prostate-specific antigen, *PTHrP* parathyroid hormone-related protein, *RANK* receptor activator of nuclear factor kappa B, *RANKL* receptor activator of nuclear factor kappa B ligand, *SPARC* secreted protein acidic and cysteine rich, *TGF* transforming growth factor beta, *VEGF* vascular endothelial growth factor, *Wnt1* wingless-type MMTV integration site family member 1

A summary of the key factors contributing to the development of hypercalcaemia and hypocalcaemia, by primary tumour, is presented in Table 1.

Hypercalcaemia of malignancy

Previous estimates of hypercalcaemia of malignancy reported that it occurred in 5–30% of patients with cancer [30]. However, prevalence rates have fallen progressively with the widespread, early and prolonged use of agents that inhibit bone resorption [31, 32]. A recent observational study in patients with cancer of any type or stage found that the 2012 hypercalcaemia prevalence was 0.67%; prevalence estimates varied across cancer types and were highest for individuals with lung cancer, multiple myeloma, or stage IV cancer [33]. Similarly, a recent US study reported a hypercalcaemia prevalence of 2–2.8% among all patients with cancer, ranging from 1.4–2.1% in prostate cancer, to 7.5–10.2% in multiple myeloma [34]. Furthermore, both studies examined the prevalence of hypercalcaemia in patients with cancer and not specifically hypercalcaemia of malignancy; therefore, the prevalence of true hypercalcaemia of malignancy is likely to be lower. Indeed, a study of 642 patients diagnosed with hypercalcaemia of malignancy reported that up to one third of cases were not caused by tumour-related factors [35].

Signs and symptoms of hypercalcaemia include polyuria, nausea and vomiting, constipation, weakness, obtundation, and, in severe cases, coma [30, 36]. Early symptoms can be mild and difficult to distinguish from the underlying cancer or side effects of cancer therapy. When hypercalcaemia of malignancy is suspected, blood calcium concentrations should be measured; total blood calcium concentrations, adjusted for albumin, above 10.2 mg/dL are diagnostic of hypercalcaemia [1]. It should be noted, however, that disease development and the severity of symptoms are related to both the absolute blood calcium level and to the rate of increase [1, 30, 36].

Hypercalcaemia of malignancy can occur in patients with or without osteolytic bone metastases and is thus classified as

Table 1 Summary of incidence of and mechanisms underlying calcium imbalance, by malignancy [1, 27–29]

Malignancy	Hypercalcaemia	Hypocalcaemia
Prostate	• Prostate cancer accounts for only ~3% of cases of hypercalcaemia of malignancy. Therefore, hypercalcaemia is very rare in this patient population • Strong association with bone metastases, although these are not typically osteolytic	• High risk of hypocalcaemia. Low calcium levels have been reported to occur in up to 30% of patients with advanced prostate cancer • Strong association with bone metastases, which are most commonly osteoblastic • Grade ≥ 2 hypocalcaemia might be expected in 6–21% of patients treated with inhibitors of bone resorption • Prostate cancer is a risk factor for development of grade ≥ 2 hypocalcaemia during treatment with inhibitors of bone resorption
Breast	• Breast cancer accounts for ~25% of cases of hypercalcaemia of malignancy • Strong association with bone metastases, which are typically osteolytic • PTHrP is an important mediator of hypercalcaemia in both metastatic and non-metastatic breast cancer	• Hypocalcaemia might be expected in 6–8% of patients treated with inhibitors of bone resorption
Lung	• Lung cancer accounts for ~35% of cases of hypercalcaemia of malignancy • Can be associated with bone metastases, which may be osteolytic • PTHrP may be an important mediator of paraneoplastic hypercalcaemia • Rare reports of ectopic tumour-produced PTH associated with hypercalcaemia	• Hypocalcaemia might be expected in 3–18% of patients with lung cancer treated with inhibitors of bone resorption • SCLC is a risk factor for development of grade ≥ 2 hypocalcaemia during treatment with inhibitors of bone resorption
Haematological	• Haematological cancers account for ~14% of cases of hypercalcaemia of malignancy • Bone metastases are typically osteolytic, associated with risk of hypercalcaemia • PTHrP and 1,25-$(OH)_2D_3$ may be important mediators of hypercalcaemia	• Hypocalcaemia might be expected in 8–13% of patients with multiple myeloma treated with inhibitors of bone resorption
Renal	• Renal cancer accounts for ~3% of cases of hypercalcaemia of malignancy • Bone metastases, which may be osteolytic, associated with risk of hypercalcaemia • PTHrP may be a mediator of hypercalcaemia	• Risk of hypocalcaemia with inhibitors of bone resorption

PTHrP parathyroid hormone-related protein, *SCLC* small-cell lung cancer

osteolytic or humoral, respectively [32, 37]. Elevation of circulating PTHrP level has a central role in the pathogenesis of both humoral and osteolytic hypercalcaemia of malignancy [26]. A study of 30 patients with solid tumours and humoral hypercalcaemia of malignancy revealed that up to 80% of individuals had raised plasma PTHrP concentrations compared with healthy controls [38]. Elevated circulating PTHrP levels have also been reported in 65% of patients with bone metastases and hypercalcaemia [39].

Although hypercalcaemia of malignancy often occurs with metastatic bone disease, there is no clear correlation between the extent of bone metastases and the development or severity of hypercalcaemia [40]. This is probably because osteolytic and humoral factors can be present together; a study of 443 patients with cancer and hypercalcaemia showed that 53% of patients had osteolytic hypercalcaemia, 35% had humoral hypercalcaemia, and 12% had both osteolytic and humoral factors [35]. Furthermore, renal function and the extent of renal tubular calcium resorption also affect blood calcium levels [30].

Hypercalcaemia is associated with poor prognosis. Median survival has been shown to be only 52 and 54 days for patients with mixed solid tumours [41] or colorectal cancer [42], respectively, increasing to 3.5 months in lung cancer [43] and 4.5 months in breast cancer [44]. Furthermore, there are data suggesting that the underlying pathology of hypercalcaemia of malignancy adversely influences prognosis; a prospective case series of 76 individuals with hypercalcaemia of malignancy showed that, for those aged 65 years or older, mortality was higher in patients with higher pretreatment blood calcium and elevated PTHrP levels than in those with lower calcium and normal PTHrP levels [45].

Benign causes of hypercalcaemia should also be considered when diagnosing patients with cancer. To confirm a diagnosis of hypercalcaemia, blood calcium (adjusted for albumin) and PTH concentration should be measured. If PTH levels are not supressed then primary hyperparathyroidism must be suspected. Vitamin D (25(OH) vitamin D) should also be measured to eliminate excess vitamin D as the cause of hypercalcaemia [46]. Hyperparathyroidism has been shown to be a predominant non-malignant cause of hypercalcaemia and so requires a different treatment strategy. Other causes of hypercalcaemia are much less frequent than hyperparathyroidism [35]. Therefore, in order to optimise the care of patients with cancer and hypercalcaemia, it is important to exclude other causes, which are mainly primary hyperparathyroidism and, more rarely, excess vitamin D.

Treatment of hypercalcaemia of malignancy

The most effective therapy for patients with hypercalcaemia of malignancy is treatment of the underlying cancer in order to reduce tumour production of factors that promote bone resorption and renal tubular calcium reabsorption; however, this may not be possible or effective in patients with advanced cancer [36]. Therapies that inhibit bone resorption and promote renal calcium excretion therefore become important. Most patients with hypercalcaemia of malignancy are dehydrated at presentation and rehydration is often the first step of treatment. Saline should be given at a maximal initial rate of 200–300 mL/h, then adjusted to maintain a urine output of 100–150 mL/h [46]. This, however, relieves the symptoms rather than addressing the underlying disease, and therefore, rehydration alone rarely resolves hypercalcaemia [47]. Nearly all patients with hypercalcaemia of malignancy have increased osteoclastic bone resorption; hence, inhibition of bone resorption is a key target for management of the condition [1].

Bisphosphonates, the first class of agents that inhibit bone resorption, are synthetic analogues of pyrophosphonate (a natural regulator of bone metabolism) and are preferentially localised to the extracellular bone matrix. From there, bisphosphonates may inhibit the differentiation of osteoclastic precursors, induce apoptosis of osteoclasts and stimulate the release of osteoclastic inhibitory factors from osteoblasts [48]. The bisphosphonates commonly used to correct hypercalcaemia are clodronate, pamidronate, ibandronate and zoledronic acid [49]. Zoledronic acid (a nitrogen-containing bisphosphonate), at a dose of 4 mg infused over 15 min, is approved in the USA and the European Union for the treatment of hypercalcaemia of malignancy and the prevention of skeletal-related events (SREs) in patients with bone metastases [50, 51]. At this approved dose, zoledronic acid will lead to a reduction in blood calcium concentration within 2–3 days of administration [46]. Zoledronic acid was shown to have greater efficacy than pamidronate in the treatment of hypercalcaemia of malignancy in a pooled analysis of two randomised, double-blind, phase 3 trials involving 275 patients with moderate-to-severe hypercalcaemia of malignancy. Treatment with zoledronic acid resulted in a significantly higher proportion of complete responses by day 10 (88.4 versus 69.7%; $P = 0.002$) (Fig. 2a), more rapid calcium normalisation, and more durable responses than treatment with pamidronate [52]. Renal adverse events were more frequent, however, in the patients receiving zoledronic acid; it is, therefore, not recommended if creatinine clearance is less than 30 mL/min [50]. Ibandronate, also a nitrogen-containing bisphosphonate, has been successfully used, notably in patients with myeloma and renal failure [54]. Although not currently indicated for the treatment of hypercalcaemia of malignancy, ibandronate may offer an alternative therapy for patients with renal failure [55].

More than 90% of patients with hypercalcaemia of malignancy can be successfully treated with rehydration and bisphosphonates; however, some patients do not respond to or experience relapse on bisphosphonate therapy. Persistent or relapsed hypercalcaemia of malignancy remains a difficult

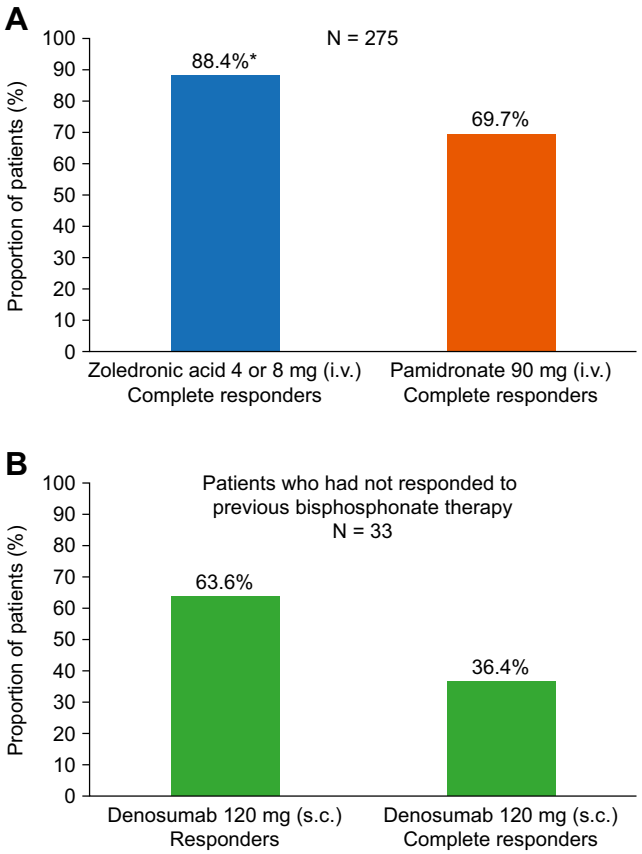

Fig. 2 Responses to treatment with bisphosphonates or denosumab. **a** Proportion of patients demonstrating a complete response at day 10 in a pooled analysis of two randomised, double-blind phase 3 trials of patients with moderate-to-severe hypercalcaemia of malignancy who received zoledronic acid or pamidronate (N = 275). Complete response was defined as CSC ≤ 10.8 mg/dL (2.7 mmol/L). [52]. **b** Proportion of patients demonstrating a response or complete response at day 10 in a single-arm, open-label study of patients who had hypercalcaemia of malignancy (CSC levels >12.5 mg/dL [3.125 mmol/L]) despite receiving bisphosphonate treatment. During the study, patients (N = 33) received denosumab 120 mg s.c. and response was defined as CSC < 11.5 mg/dL (2.9 mmol/L; CTCAE grade 0 or 1). Complete response was defined as CSC ≤ 10.8 mg/dL (2.7 mmol/L). [53]. *P = 0.002 versus pamidronate. *CSC* albumin-corrected serum calcium, *CTCAE* Common Terminology Criteria for Adverse Events, *i.v.* intravenous, *s.c.* subcutaneous

complication to manage [56]. Denosumab, a fully-human IgG2 monoclonal antibody against RANKL that disrupts signalling through RANK and prevents tumour-mediated activation of osteoclasts [57], has been shown to be effective for the treatment of patients with bisphosphonate-refractory hypercalcaemia. In a single-arm, open-label study, 33 patients with hypercalcaemia of malignancy despite recent bisphosphonate treatment received denosumab 120 mg on days 1, 8, 15, and 29, and then every 4 weeks. In total, 64% of patients responded to denosumab treatment by day 10, with 36% of patients experiencing a complete response (Fig. 2b) [53]. The results of this study formed the basis of the approval of denosumab for the treatment of bisphosphonate-refractory hypercalcaemia of malignancy in the USA, Australia, Canada, and Russia [58–61]. Denosumab, therefore, offers a new treatment option for patients with persistent hypercalcaemia that does not respond to bisphosphonates or hypercalcaemia that relapses following bisphosphonate treatment.

Inhibitors of bone resorption are used to prevent SREs, which are associated with substantial pain and morbidity [62], in patients with metastatic bone disease [50, 63]. The risk of SREs is high in these patients, with up to 64% of those with advanced breast, prostate or lung cancer experiencing an SRE [64–67]. Furthermore, many patients experience multiple SREs over the course of their disease; individuals with breast cancer can experience a mean of 3.7 SREs per year, if left untreated [64]. Adequate preventive treatment is, therefore, a priority. Denosumab has shown superiority over zoledronic acid in preventing SREs in patients with bone metastases [68]. There is also preliminary evidence suggesting that denosumab may offer advantages over zoledronic acid in terms of delaying the onset of and reducing the occurrence or risk of hypercalcaemia of malignancy. A post hoc analysis of data from two phase 3, randomised, controlled trials comparing denosumab and zoledronic acid for the prevention of SREs in patients with bone metastases demonstrated that denosumab significantly delayed the time to first on-study hypercalcaemia event by 37% (hazard ratio, 0.63; 95% confidence interval (CI), 0.41–0.98; P = 0.042). Furthermore, fewer patients receiving denosumab experienced such an event (1.7% compared with 2.7% of those receiving zoledronic acid; P = 0.028), and treatment with denosumab reduced the risk of developing recurrent hypercalcaemia of malignancy by 52% compared with zoledronic acid (rate ratio, 0.48; 95% CI, 0.29–0.81; P = 0.006) [69–71]. These data must be interpreted cautiously, however, as neither study was powered to look for statistically significant differences in the occurrence of hypercalcaemia between the study arms. Despite this, denosumab may be considered to be a more potent inhibitor of bone resorption than zoledronic acid and may offer a superior option to prevent hypercalcaemia of malignancy. Denosumab also offers further advantages in that it is administered subcutaneously rather than intravenously, and it may be useful in patients with renal insufficiency.

In patients with severe hypercalcaemia, the hormone calcitonin is an important adjunctive treatment that acts within 4 h of administration and can be used to immediately reduce calcium plasma concentrations. Calcitonin reduces calcium concentration by inhibiting osteoclast activity and increasing renal calcium clearance. It should be given at a dose of 4–8 units/kg subcutaneously or intramuscularly every 6–12 h; duration of dosing is, however, limited to 48 h owing to the development of tachyphylaxis and decreased responsiveness [46].

Currently, the standard treatment for hypercalcaemia of malignancy is rehydration combined with intravenous

bisphosphonate therapy, with zoledronic acid preferred over pamidronate [36, 52]. In some countries, denosumab is approved for use in patients with bisphosphonate-refractory hypercalcaemia [53]. In addition, calcitonin may be useful for patients with severe or life-threatening hypercalcaemia because it causes a rapid, albeit transient, decrease of high serum calcium levels [46, 72].

Hypocalcaemia

Hypocalcaemia can cause muscle spasms, irritability, tetany, paraesthesias, seizures, and cardiac dysrhythmias. Its incidence is difficult to estimate because the aetiology is multifactorial. Defined as corrected total blood calcium below 8.5 mg/dL or ionised blood calcium below 4.6 mg/dL, hypocalcaemia occurs in approximately 30% of all patients with advanced prostate cancer [27, 28]. In patients with osteoblastic bone metastases, excessive uptake of calcium by bone-forming metastases, which sequester calcium, is a primary cause of hypocalcaemia [73]. Renal insufficiency can also contribute to the development of low blood calcium levels [74, 75].

The use of inhibitors of bone resorption for the prevention of SREs in patients with metastatic bone disease may induce or worsen hypocalcaemia, both in patients with prostate cancer [76–78] and patients with other tumours that metastasise to bone [29, 79, 80]; individuals with prostate cancer and osteoblastic metastases are most at risk of developing hypocalcaemia as an adverse effect of such treatment. Other risk factors include high baseline levels of bone turnover markers (urinary N-telopeptide of type I collagen and bone-specific alkaline phosphatase) and reduced creatinine clearance (Table 2) [29]. Bisphosphonates and denosumab prevent bone resorption by inhibiting osteoclast activity and thus diminish calcium mobilisation as a consequence of bone turnover. Treatment with inhibitors of bone resorption may also cause a shift of calcium into the bone if large populations of osteoblasts exist, as in osteoblastic metastases [81, 82], or when there is excess osteoid tissue (e.g. as a consequence of long-term vitamin D deficiency) [29]. Hypocalcaemia occurs more frequently in patients receiving denosumab than in those receiving zoledronic acid (Fig. 3); a combined analysis of three phase 3 trials comparing denosumab and zoledronic acid reported hypocalcaemia of grade 3 or higher in 3.1% and 1.3% of patients in the denosumab and zoledronic acid groups, respectively [83]. By contrast, an open-label extension of two of these trials, in which 295 patients received monthly denosumab for more than 3 years, reported similar rates of hypocalcaemia: 4.6% of patients who had received denosumab and 3.1% of patients who switched from zoledronic acid to denosumab experienced hypocalcaemia [84]. Thus, hypocalcaemia associated with denosumab appears to occur most often during the initial stages of therapy, but 'stabilises' thereafter and does not seem to increase with increased duration of exposure [29]. The increased risk of hypocalcaemia seen with denosumab is consistent with it being a more potent inhibitor of bone resorption than zoledronic acid [29]. Hypocalcaemia associated with treatment with inhibitors of bone resorption is often mild and transient, but can be severe, with some patients requiring hospitalisation and clinical intervention [79]. Hypocalcaemia must, therefore, be prevented wherever possible and managed in the context of the current management of metastatic bone disease.

Treatment and prevention of hypocalcaemia

Hypocalcaemia in patients with cancer can have severe consequences, whether occurring with or without the use of inhibitors of bone resorption, but responds well to calcium and

Table 2 Factors significantly associated with the risk of developing grade ≥ 2 hypocalcaemia among denosumab-treated patients participating in three identically designed phase 3 trials of denosumab 120 mg s.c. ($N = 2841$) versus zoledronic acid 4 mg i.v. ($N = 2836$). Adapted with permission from Body JJ et al. *Eur J Cancer* 2015 [29]

Demographic variable/baseline disease characteristic	Denosumab		
	Point estimate	95% CI	*P* value
Sex (male versus female)	0.761	0.459–1.262	NS
Tumour type – prostate cancer	2.193	1.210–3.974	0.0096
Tumour type – SCLC	4.982	2.252–11.021	<0.0001
Baseline creatinine clearance (30 to < 60 mL/min versus ≥ 60 mL/min)	1.414	1.039–1.924	0.0276
Baseline corrected uNTx level (> 50 nmol/mmol versus ≤ 50 nmol/mmol)	1.305	1.018–1.673	0.0360
Baseline BSAP level (> median versus ≤ median; 20.77 μg/L)	1.734	1.280–2.348	0.0004
Number of bone metastases (> 2 versus ≤ 2)	0.631	0.312–1.275	NS
Interaction between baseline BSAP and number of bone metastases	2.419	1.154–5.071	0.0193
Type of lesion – osteoblastic	1.197	0.870–1.647	NS

BSAP bone-specific alkaline phosphatase, *CI* confidence interval, *i.v.* intravenous, *NS* not significant, *s.c.* subcutaneous, *SCLC* small-cell lung cancer, *uNTx* urinary N-telopeptide of type I collagen

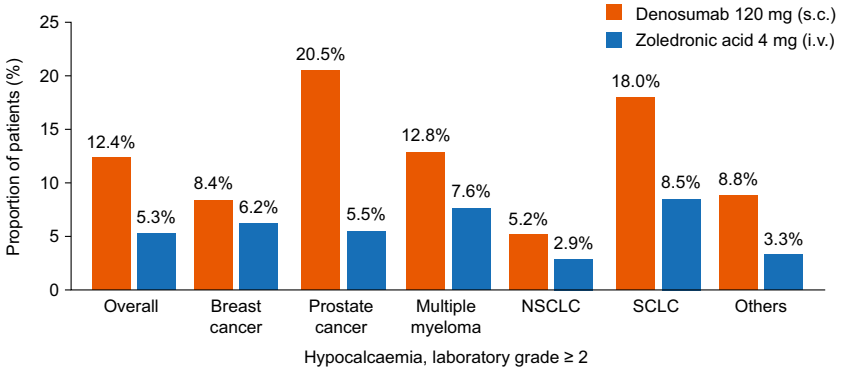

Fig. 3 Incidence of laboratory grade ≥ 2 hypocalcaemia by tumour type. Reproduced with permission from European Journal of Cancer, Vol: 51, Body JJ et al. Pages: 1812–1821 (http://dx.doi.org/10.1016/j.ejca.2015.05.016) Copyright (2015), with permission from Elsevier (https://creativecommons.org/licenses/by-nc-nd/2.0/) [29]. *NSCLC* non-small-cell lung cancer, *SCLC* small-cell lung cancer

vitamin D supplementation [74, 80, 85, 86]. Furthermore, when treatment with inhibitors of bone resorption is required for the management of metastatic bone disease, hypocalcaemia can usually be prevented by identification and appropriate management of at-risk patients [29]. Case reports and retrospective analyses have identified a number of risk factors associated with the development of hypocalcaemia in those receiving inhibitors of bone resorption; these include vitamin D deficiency, renal insufficiency, osteoblastic metastases, prostate cancer, and low baseline blood calcium levels (Table 2) [29, 78–80]. It is therefore important that vitamin D and calcium levels are assessed and supplementation initiated before starting treatment with inhibitors of bone resorption. This evaluation is particularly important given the high prevalence of vitamin D insufficiency or deficiency among patients with metastatic cancer [87]. Furthermore, all patients receiving inhibitors of bone resorption for the prevention of SREs should receive concomitant calcium and vitamin D supplementation; use of these supplements has been shown to lower the risk of developing hypocalcaemia by 27% and 40% in patients receiving zoledronic acid or denosumab, respectively [29]. An interim analysis of an open-label observational study of treatment persistence in patients with cancer who were receiving denosumab to prevent SREs found that most patients (80%) received calcium and vitamin D supplementation at the start of denosumab treatment. Long-term follow-up persistence data, however, are not yet available [88]. Previous reports suggest that adherence to calcium and vitamin D supplementation is low [89]; patients should, therefore, be counselled on the importance of adequate calcium and vitamin D intake in order to improve adherence [90]. Use of 1,25-dihydroxyvitamin D, the active metabolite of vitamin D, might offer further advantages in the prevention and treatment of hypocalcaemia; however, trials are required to confirm this.

Although hypocalcaemia can occur at any time during treatment with inhibitors of bone resorption, studies show that it often develops soon after treatment initiation; within 7 days, in some cases [79, 91]. Therefore, careful monitoring of at-risk patients after starting treatment is important to enable quick detection and resolution of hypocalcaemia [79, 91]. At-risk patients should also be educated about the symptoms of hypocalcaemia and encouraged to report any indicative symptoms [29]. If hypocalcaemia occurs while a patient is receiving inhibitors of bone resorption, additional calcium and vitamin D supplementation and further monitoring are advised. Delaying the administration of inhibitors of bone resorption because of hypocalcaemia is rarely necessary.

Conclusion

Both hypercalcaemia and hypocalcaemia can lead to serious complications in patients with advanced cancer. Bisphosphonates are effective treatments for both osteolytic and humoral hypercalcaemia of malignancy. In patients with persistent or relapsed hypercalcaemia of malignancy that fails to respond or no longer responds to bisphosphonate treatment, denosumab offers a therapeutic option and, as such, has been approved for this indication in the USA, Australia, Canada, and Russia. Denosumab is a more potent inhibitor of bone resorption than zoledronic acid and is more effective at preventing hypercalcaemia. It is possible that the incidence of hypercalcaemia of malignancy may further decrease as potent inhibitors of bone resorption are used more commonly and earlier in the course of management of patients with metastatic cancer. On the other hand, inhibitors of bone resorption have been shown to increase the risk of developing hypocalcaemia. This risk is higher with denosumab than with zoledronic acid; however, it can be managed by proper identification of at-risk patients and careful monitoring of those receiving these agents. Given the potential improvements to quality of life that inhibitors of bone resorption offer patients with advanced cancer, the benefits and risks associated with their use must be assessed. Further to this, physicians need to be aware of the measures they can take to counteract these

risks and to find the balance between hypercalcaemia and hypocalcaemia.

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Compliance with ethical standards

Conflicts of interest J-JB has served as a consultant for and received lecture fees from Amgen. DN is an employee and shareholder of Amgen. GT has served on advisory board for Celgene, Novartis and Roche.

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