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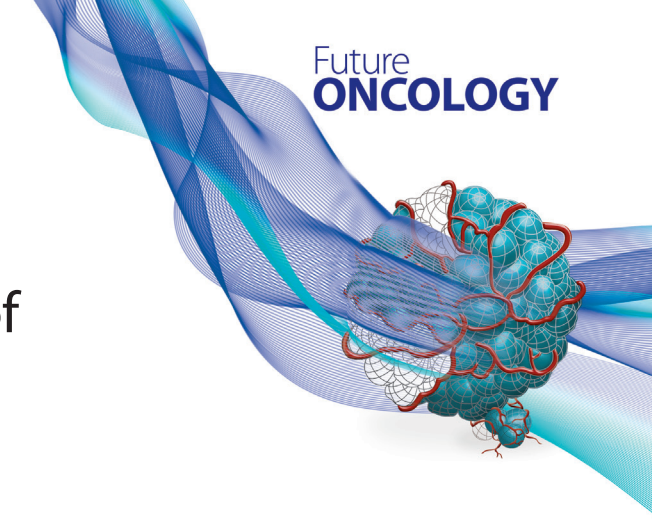

DRUG EVALUATION

Denosumab: a new agent in the management of hypercalcemia of malignancy

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Hypercalcemia of malignancy is an oncologic emergency due to tumoral factors that stimulate osteoclast-mediated bone resorption. It requires a combination of recommended treatments (i.e., hydration, bisphosphonate and calcitonin), which may be deleterious in patients with compromised cardiac or renal function or may not control serum calcium levels long term. Recurrent or refractory hypercalcemia may preclude the use of chemotherapeutic agents needed to effectively treat the underlying cancer, which is the cause of hypercalcemia. Denosumab, a fully human monoclonal antibody against RANKL, inhibits the maturation, function and survival of osteoclasts. An open-label, single-arm study of denosumab in patients with hypercalcemia of malignancy despite recent bisphosphonate treatment revealed positive results. Thus, the US FDA recently approved denosumab for the indication of hypercalcemia of malignancy, increasing the options available for patients with this debilitating and life-threatening condition.

KEYWORDS
• cancer • denosumab • hypercalcemia of malignancy • RANKL inhibition • treatment

Hypercalcemia of malignancy (HCM), the most common paraneoplastic syndrome, occurs in 20–30% of patients at some point during the course of their advanced cancer [1,2]. While it has been associated with almost all cancer subtypes, the most common cancers associated with hypercalcemia include breast cancer, lung cancer and multiple myeloma. It is associated with a wide spectrum of symptoms including nausea, vomiting, anorexia, abdominal pain, constipation, polyuria, hypotension, bone pain, fatigue and confusion [2]. Renal failure or coma can occur; thus, HCM is considered an oncologic emergency. HCM is a poor prognostic indicator for cancer patients, with an estimated median survival rate reported to be between 30 days and 2–3 months regardless of active treatment [2–4].

The definitive method to control HCM is to treat the underlying cancer with systemic chemotherapy, surgical resection or targeted radiation as appropriate to the clinical setting. However, severe hypercalcemia that compromises renal or cardiovascular function can preclude the implementation of such antitumoral treatments, and consequentially decrease odds of survival. Available antihypercalcemic treatments are temporary measures for controlling hypercalcemia to allow patients to tolerate essential cancer-specific treatments. This review describes the pathogenic mechanisms mediating HCM and strategies for managing HCM, highlighting the recent addition of denosumab to the armamentarium of available agents.

Pathophysiology of hypercalcemia of malignancy

The etiology of hypercalcemia associated with cancer occurs through various mechanisms that can broadly be divided into two major categories, both of which stimulate osteoclast-mediated bone

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resorption causing release of calcium out of the bone into the serum. The first and most common type (80% of cases) is due to secretion of parathyroid hormone-related protein (PTH-rP) by the cancer cells, called humoral hypercalcemia of malignancy (HHM) [2]. HHM is most often associated with squamous cell malignancies of the lung, head and neck, esophagus, skin or cervix or carcinomas of the breast, kidney, prostate or bladder. There is little to no bone metastases present [1]. The aminoterminus region of PTH-rP is homologous to that of natural PTH, thus, mimicking its actions on bone metabolism. PTH-rP production by the cancer cells causes osteoblast precursors to express RANKL, which binds to the RANK receptor on osteoclast percursors. This interaction between RANKL and RANK enables the maturation of osteoclast precursors into active osteoclasts, which mediate bone resorption and release of calcium and phosphorus into circulation [4–6]. The second type, accounting for approximately 20% of cases of hypercalcemia, is due to local osteolysis mediated by malignant cells in the bone marrow producing osteoclast-activating cytokines (e.g., macrophage inflammatory protein-1 alpha, IL-1, IL-6, TNF-α, RANKL) [1,7]. Local osteolysis is most commonly associated with multiple myeloma, breast cancer and lymphoma and is associated with a significant burden of bone metastases.

A less common mechanism of HCM is the excessive production of 1,25-dihydroxyvitamin D (or calcitriol) typically associated with lymphomas but also reported with squamous cell carcinoma of the tongue, ovarian cystadenocarcinoma and chronic lymphocytic leukemia. Excessive calcitriol production by tumor cells leads to an increased absorption of both calcium and phosphorus from the intestinal tract and osteoclast-mediated bone resorption [8]. An even more rarely reported cause of HCM is the ectopic production of authentic PTH by tumoral cells [1,9].

Long-standing treatment strategies for HCM

To date, there are no guidelines available regarding the management of HCM. Beyond treating the underlying malignancy, general practice recommendations are to implement a series of strategies or agents to correct the volume depletion and hypotension due to calciuresis and polyuria, increase urinary calcium excretion and inhibit osteoclast activity **(Table 1)** [10]. Initiating aggressive fluid replacement (0.9% saline) is essential to manage dehydration and prerenal azotemia, which in turn will increase the glomerular filtration rate and excretion of calcium. A recommended goal is to achieve urine output of >75 ml/h while monitoring for volume overload, especially in patients with a history of congestive heart failure [11]. Loop diuretics have been commonly used in euvolemic patients in conjunction with saline infusion based on the premise of promoting urinary excretion of calcium, although this strategy has not been well established in clinical trials and can lead to secondary electrolyte abnormalities [12]. Thus, the routine use of a loop diuretic is not recommended, unless diuresis is needed in a patient who develops fluid overload from intravenous (iv.) fluids [11].

Synthetic salmon calcitonin (4–8 units/kg intramuscularly or subcutaneously [sc.] every 12 h) interferes with osteoclast function, stimulates osteoblast activity, increases renal calcium excretion and inhibits calcium reabsorption by the intestines [14]. It has a rapid onset of action (2 h) and is degraded by the kidney, without causing nephrotoxicity [13]. While it is useful when combined with iv. hydration for initial treatment of hypercalcemia especially in patients with acute kidney injury, its use is limited due to a short duration of efficacy, mild and transient reduction of calcium levels and potential development of tachyphylaxis from downregulation of calcitonin receptors on osteoclasts and eventual reduction in effect [11]. The FDA approved it for the management of HCM in 1980.

Bisphosphonates (BPs) are synthetic analogs of pyrophosphate that bind the surfaces of bone at sites undergoing active resorption. When osteoclasts interact with BP-coated bone, there is disruption of actin attachment sites, which prevents osteoclast adherence needed for continued resorption [15]. Moreover, BPs promote apoptosis of osteoclasts [16] and decrease recruitment and development of progenitor cells resulting in overall decrease in osteoclast number. In addition, BPs stimulate expression of osteoprotegerin (OPG), a decoy receptor for RANKL, which prevents RANKL binding to the RANK receptor on osteoclast precursors, thereby inhibiting osteoclast cell maturation. The current data on the overall effect of BPs on osteoblast activity are more conflicting. *In vitro* mouse and human models have shown that BPs induce osteoblast precursor proliferation and inhibit apoptosis [17] while studies utilizing primary human osteoblast cultures from osteoporotic patients suggest that BPs have different biochemical effects dependent on dosage [18].

Table 1. Treatments for hypercalcemia of malignancy.

Agent	Mechanism of action	Dose	Onset of action	Duration of action	Notable adverse reactions
Saline infusion	Volume repletion; increases renal excretion of Ca	200–500 ml/h (goal urine output >75 ml/h)	Within 6 h	Hours	Volume overload
Calcitonin	Inhibits OC activity; increases renal excretion of Ca; inhibits GI absorption of Ca	4–8 units/kg im./sc. every 12 h for 2–3 days	≈ 2 h	6–8 h	Nausea Local site reaction Flushing Hypersensitivity Hypocalcemia
Pamidronate	Inhibits OC activity	60–90 mg iv. over 2–6 h[†] (one dose)[‡]	≤24 h	7–14 days	Fever Hypocalcemia Hypophosphatemia Nephrotoxicity ONJ
Zoledronic acid	Inhibits OC activity	4 mg[§] iv. over 15–30 min[†] (one dose)[‡]	24–48 h	32 days	Same as pamidronate
Denosumab	Inhibits RANKL binding to RANK	120 mg sc. every 4 weeks + loading doses on days 8/15	9 days (median time to response[¶])	104 days (duration of response[¶])	Fatigue Hypophosphatemia Hypocalcemia Nausea Dermatitis/rash ONJ

[†]Use a longer infusion time in patients with lower glomerular filtration rate.
[‡]Wait at least 7 days to pass before re-treatment.
[§]Adjust dose for zoledronic acid based on creatinine clearance using the Crockcroft-Gault formula.
[¶]Response defined as a corrected serum calcium less than or equal to 11.5 mg/dl.
Ca: Calcium; GI: Gastrointestinal; im.: Intramuscularly; iv.: Intravenously; OC: Osteoclast; ONJ: Osteonecrosis of the jaw; sc.: Subcutaneously.
Data taken from [13].

The iv. BPs approved for use in treatment of malignancy-associated hypercalcemia include pamidronate (approved in 1991) and zoledronic acid (approved in 2001). Results pooled from Phase III trials have shown zoledronic acid to be more potent than pamidronate with faster normalization of calcium levels, longer duration of calcium control and a higher response rate [19]. Although iv. BPs have a slow onset of action (24–72 h), the duration of therapeutic action is long (~30 days for zoledronic acid and 20 days for pamidronate) [20]. Though usually well tolerated, side effects from iv. infusion of BPs include flu-like symptoms, impaired renal function, hypocalcemia and hypophosphatemia, especially in patients with vitamin D deficiency. The use of iv. BPs is limited in patients with compromised renal function, due to drug-induced nephrotoxicity; thus, dose reduction is required in patients with glomerular filtration rate less than 60 ml/min. Prolonged dosing with potent iv. BPs increases the risk of rare complications such as osteonecrosis of the jaw and atypical femoral fractures [21].

Corticosteroids are useful in HCM mediated by ectopic production of calcitriol seen in some lymphoma patients. By inhibiting 1-alpha-hydroxylase, steroids (hydrocortisone, prednisone) will prevent the conversion of precursor 25-hydroxyvitamin D into calcitriol [8]. Additionally, in such cases of vitamin D-mediated hypercalcemia, restriction of dietary calcium is needed. For patients with severe renal insufficiency and oliguria, aggressive hydration and diuresis may not be possible and hemodialysis with a low calcium bath may be necessary.

Denosumab: the new kid on the block for HCM

Denosumab is a fully human monoclonal antibody that binds to RANKL to prevent ligand interaction with RANK receptors on precursor osteoclasts, thus, interfering with osteoclast maturation, function and survival [22]. Consequently, bone resorption is reduced. This agent is approved by the FDA for the treatment of postmenopausal women and men with osteoporosis, and cancer treatment-related bone loss (dosing regimen – 60 mg sc. every 6 months). It is also FDA approved for the prevention of skeletal-related events in patients with metastatic bone disease from solid tumors and patients with

unresectable giant cell tumor of bone (dosing regimen – 120 mg sc. every 4 weeks).

In clinical trials, denosumab decreased the incidence of skeletal-related events or HCM in patients with advanced solid-organ cancers with bone metastases [23–26]. In a preclinical study investigating OPG in murine models of PTH-rP-mediated HHM, RANKL inhibition with a single injection of OPG caused a rapid reversal of hypercalcemia [27]. The rate of normalizing calcium and duration of action were greater with OPG administration than with pamidronate or zoledronic acid. Since 2012, there have been numerous case reports reporting the effectiveness of denosumab in patients with cancer-associated hypercalcemia in tumors including multiple myeloma, renal cell carcinoma and ovarian cancer and parathyroid carcinoma [28–35].

Given these findings and recognizing that some patients with HCM either do not respond to or do not have sustainable responses to iv. BP therapy, denosumab was evaluated in a single-arm multicenter, international Phase II study for the treatment of patients with BP-refractory HCM, as defined by hypercalcemia (albumin-corrected serum calcium [CSC] >12.5 mg/dl) despite receiving iv. BP treatment >7 and ≤30 days prior to screening [10,36]. The primary endpoint was the proportion of patients with a response of CSC ≤11.5 mg/dl (Common Terminology Criteria for Adverse Events grade ≤1) by day 10. A complete response was defined as a CSC ≤10.8 mg/dl. The study group of 33 patients with solid (breast [n = 6], neuroendocrine [n = 4], non-small-cell lung (n = 3), renal cell (n = 3), head and neck (n = 2) and one each for bladder/liver/ovarian/small-cell lung/sarcoma/adenocarcinoma of unknown primary) or hematologic malignancies received denosumab 120 mg sc. on day 1 and every 4 weeks afterward, with two additional doses on days 8 and 15 to reach steady-state concentrations. By day 10, 64% of the patients (n = 21) responded with a CSC ≤11.5 mg/dl, while 33% (n = 12) had a complete response. During the course of the study, 70% (n = 23) and 64% (n = 21) had a response (CSC ≤11.5 mg/dl) and a complete response (CSC ≤10.8 mg/dl), respectively. Although the confidence intervals of these proportions were not described in the manuscript, a striking and clinically significant finding in this study was that in this population with aggressive disease, as demonstrated by having Common Terminology Criteria for Adverse Events grade 3 hypercalcemia within a median of 17 days from last iv. BP dose prior to denosumab, the median duration of response to denosumab (time from initial response to last day when CSC ≤11.5 mg/dl) was 104 days. The most common adverse events (AEs) reported were nausea (30%), dyspnea/headache/peripheral edema/vomiting (24% each) and constipation/anorexia/diarrhea (21% each). Treatment-related AEs were reported as hypophosphatemia and nausea (12% each). Two serious AEs (cardiac arrest and colitis, one patient each) were considered treatment-related. This study had several limitations, including small sample size and a short follow-up time period, thus, preventing any prediction of survival advantage for patients with refractory HCM treated with denosumab. As this included a specific population of patients who had continued or recurrent hypercalcemia after iv. BP use, the use of denosumab as a first-line agent for HCM cannot be recommended based on this study. Finally, the attribution of adverse effects can be confounded by the underlying advanced cancers present in this study population. Based on these reported findings, the FDA approved denosumab for the indication of HCM refractory to BP therapy in December 2014.

An *ad hoc* pooled analysis of two Phase III, randomized, double-blinded trials of denosumab (n = 1912) or zoledronic acid (n = 1910) for patients with breast cancer, other solid tumors (excluding prostate cancer) or multiple myeloma was performed to compare the effect of each drug on preventing or delaying the onset of HCM, as defined by a CSC of >11.5 mg/dl [37]. End points were time to first on-study HCM, time to first and subsequent on-study HCM, proportion of patients experiencing HCM and proportion of patients experiencing recurrent events of HCM. Denosumab significantly delayed the time to first on-study HCM compared with zoledronic acid (HR: 0.63; 95% CI: 0.41–0.98; p = 0.042). The risk of developing recurrent HCM was reduced with denosumab by 52% (rate ratio: 0.48; 95% CI: 0.29–0.81; p = 0.006). Patients treated with denosumab had a statistically significant decrease in developing HCM (1.7%) compared with patients treated with zoledronic acid (2.7%). The overall AE and SAE rates were similar between the two treatment groups.

Denosumab can lead to hypocalcemia, especially in patients with vitamin D deficiency, severe renal impairment (creatinine clearance <30 ml/min) or on hemodialysis [38]. A recently published case series of seven patients treated

with denosumab for HCM noted that one patient developed symptomatic hypocalcemia 4 days after denosumab administration; however, this patient received a lower 60 mg dose and there was no description of the patient's vitamin D level or renal function [35]. It is also associated with osteonecrosis of the jaw (1.8% incidence) similar to that seen with iv. BPs (1.3%) [39]. It does not have nephrotoxic effects nor does it require dose adjustment based on renal function. Thus, in patients with HCM and renal impairment, denosumab may be a preferred option as front-line therapy. Further studies are required to investigate which agent would be the most effective first-line agent for HCM.

Conclusion

HCM is an oncologic emergency that causes a high burden of debilitating symptoms, conveys a poor prognosis and can limit the ability to administer necessary antitumoral treatments. Long-standing established strategies using aggressive fluid resuscitation, calcitonin and/or iv. BPs to manage the hypercalcemic episodes can be limited by comorbid conditions or sustainability of response. Denosumab, recently approved

EXECUTIVE SUMMARY

Mechanisms of action

- Denosumab is a human monoclonal antibody that binds to NF-κB ligand (RANKL) and prevents its binding to RANK receptors on osteoclasts.
- Inhibition of this interaction leads to decrease in osteoclast maturation, function and survival and reduces bone resorption and subsequent hypercalcemia.

Pharmacokinetic properties

- Denosumab has bioavailability of about 62% with subcutaneous administration.
- The median response time is 9 days with duration of response sustained for up to 104 days.
- There are no dose adjustments needed for patients with renal impairment.
- Denosumab is cleared by the reticuloendothelial system.

Clinical efficacy

- Phase II study with denosumab in patients with bisphosphonate-refractory hypercalcemia of malignancy (HCM) found 64 and 70% of patients had albumin-corrected serum calcium ≤11.5 mg/dl by day 10 and during the course of the study, respectively. 33 and 64% had corrected serum calcium ≤10.8 mg/dl by day 10 and during the course of the study, respectively.
- Phase III multicenter randomized double-blinded trial comparing efficacy of denosumab with zoledronic acid showed a statistically significant delay in time with first on-study HCM, and recurrence of HCM in patients treated with denosumab compared with zoledronic acid.

Safety & tolerability

- Denosumab can lead to hypocalcemia in patients with vitamin D deficiency, renal impairment (glomerular filtration rate ≤30 ml/min or hemodialysis) and in patients with history of hypoparathyroidism.
- Gastrointestinal side effects (nausea, vomiting, diarrhea and constipation), peripheral edema, dyspnea and anemia were reported in >20% of patients receiving treatment.
- Atypical femoral fractures and osteonecrosis of the jaw have been reported in similar rates of occurrence as with intravenous bisphosphonate therapy.
- Monitor serum calcium levels during the first weeks of initiating therapy and treat underlying vitamin D deficiency.

Drug interactions

- No formal drug–drug interaction trials conducted.

Dosage & administration

- Administer 120 mg every 4 weeks with additional 120 mg doses on days 8 and 15 on the first month of therapy.
- Administer subcutaneously in the upper arm, upper thigh and or abdomen.

for HCM refractory to BPs, is a welcome addition that effectively inhibits osteoclast-mediated bone resorption by disrupting the RANKL/RANK pathway. Ultimately, appropriate management of HCM can greatly improve a patient's quality of life and bridge the patient so that more effective agents targeting the underlying cancer can be implemented.

Disclosure

In addition to the peer-review process, with the author(s) consent, the manufacturer of the product(s) discussed in this article was given the opportunity to review the manuscript for factual accuracy. Changes were made at the discretion of the author(s) and based on scientific or editorial merit only.

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