

# Diagnosis, Pathophysiology and Management of Hypercalcemia in Malignancy: A Review of the Literature

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## ABSTRACT

Hypercalcemia of malignancy is the most common life-threatening metabolic disorder in patients with advanced stage cancers and is a sign of poor prognosis. It usually presents with markedly elevated calcium level and is severely symptomatic. It is associated with hematological malignancies, such as multiple myeloma, non-Hodgkin lymphoma, leukemias and solid cancers, particularly renal and breast carcinomas as well as squamous cell carcinomas of any organ. Several mechanisms have been implicated in the development of hypercalcemia of malignancy amongst them the osteolytic related hypercalcemia, parathyroid hormone-related peptide (PTHrP) mediated hypercalcemia, extrarenal 1,25 dihydroxyvitamin D (calcitriol) mediated hypercalcemia and parathyroid hormone (PTH) related hypercalcemia either ectopic in origin or in patients with parathyroid carcinoma. Clinical history and physical examination could point towards the correct diagnosis confirmed by the above-mentioned biochemical mediators of hypercalcemia. Early diagnosis and treatment lowering calcium levels in the blood can improve symptoms and the quality of life of these patients and avoid delays for further antitumor therapy.

## Introduction

Hypercalcemia is an uncommon finding in patients admitted to the emergency department [1, 2]. Hypercalcemia is defined as a serum calcium level above the upper limit of the normal reference range (usually above 10.5 mg/dl) and can complicate the course of 10–30% of all cancer patients [3, 4]. Among all patients who present to the emergency department with hypercalcemia, the most common causes are malignancy followed by primary hyperparathyroidism [2, 5]. The incidence of hypercalcemia at the early pre-

sensation of cancer is low (1–5%) but increases in advanced stage cancer [6] associated with poor prognosis [7] with a median duration of survival, for these patients, of 2–6 months from disease onset [7]. Among all cancers, multiple myeloma has the highest prevalence of hypercalcemia [7, 8] followed by breast, renal, and squamous carcinomas of any origin [1, 2, 9, 10]. Of the total liquid malignancies, multiple myeloma is the most prevalent hematological cancer associated with hypercalcemia, followed by leukemia and non-Hodgkin lymphoma [1, 2, 7, 11–13].

## Materials and Methods

### Review of the Literature

To identify studies and determine their eligibility a systematic research was conducted in the PubMed and Cochrane Databases on the 18<sup>th</sup> February 2019. Search terms included the following: “cancer”, “hypercalcemia”, “malignancy”, “PTHrP”, “bone lesions”, “25-OH vitamin D”, and “PTH”. The above keywords were also combined with the Boolean operators AND and OR. Two of the authors (N.A and A.A) independently examined all potentially eligible titles and abstracts. Full manuscripts were obtained as necessary to finalize eligibility (studies which were available only as abstracts were excluded). Reference lists of eligible studies were also searched through to identify additional studies. Only English language papers published in the last 10 years were selected. Studies on children (we included only adults of > 19 years old) as well as studies with hypercalcemia of non-malignant etiology (other causes such as sarcoidosis, renal failure, ileus) were also excluded. Ninety articles were finally included in our review based on the full text manuscript (► Fig. 1).

## Results

### Clinical presentation

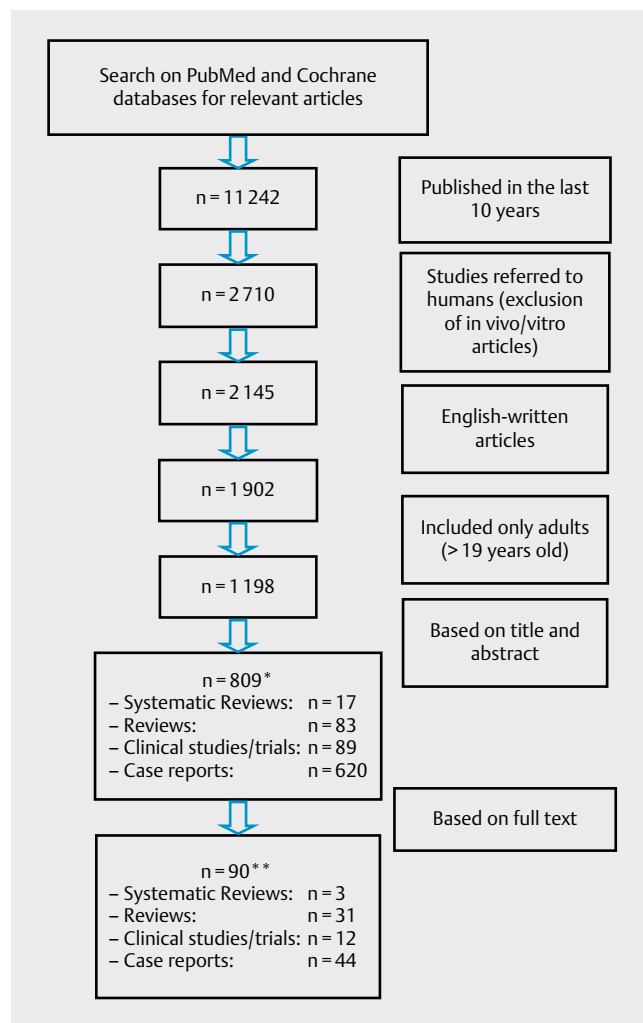
According to serum total calcium levels, hypercalcemia is categorized as follows: mild hypercalcemia 10.5–11.9 mg/dl; moderate hypercalcemia 12–13.9 mg/dl, and severe hypercalcemia  $\geq 14$  mg/dl [14]. While mild hypercalcemia may be asymptomatic, moderate to severe hypercalcemia can be associated with a variety of symptoms. Severe hypercalcemia is almost always symptomatic; it appears with an abrupt onset and is most often associated with malignancies [15]. Patients manifest gastrointestinal symptoms, such as nausea, vomiting, anorexia, constipation, abdominal pain, rarely pancreatitis, and peptic ulcer disease [16]. In addition, neurologic manifestations can also be manifested ranging from fatigue to coma, psychiatric conditions like anxiety, cognitive dysfunction, depression, as well as cardiovascular manifestations that include arrhythmias and shortening of the QT interval [17]. Renal dysfunction can be developed with polyuria, which is consistent of nephrogenic diabetes insipidus, due to kidney's impaired concentrating ability as a result of hypercalcemia [17]. Reduced oral intake of fluids due to nausea and malaise further aggravate the state of volume depletion. The clinical features of hypercalcemia are summarized in ► Table 1.

### Etiology and pathophysiology

Hypercalcemia of malignancy is most commonly caused by increased bone resorption with release of calcium from bone and the inadequate ability of the kidneys to manage higher calcium levels. There are four mechanisms, by which this can occur as depicted in ► Table 2, [17–19]:

#### Humoral hypercalcemia of malignancy (via the secretion of parathyroid hormone related peptide (PTHrP))

The concept that a PTH-like factor secreted by tumor could mediate hypercalcemia associated with malignancies with few or no



► Fig. 1 Flow diagram of the research in the databases. \* We excluded the papers referred to primary hyperparathyroidism (n = 240) or to hypercalcemia not related to malignancy (n = 119) (ex. rheumatological diseases such as sarcoidosis, chronic renal failure, hemodialysis, and ileus) as well as the papers analyzing the role of vitamin D in cancer (n = 30) without specific comment to hypercalcemia in the abstract or to the full text paper. \*\* We excluded 719 papers, 10 of them had no available full text (only abstract was available), the majority of papers (n = 679) noted hypercalcemia in the biochemical analyses of their included population without any further comment, focusing mainly on therapies of the cancer or the survival or the imaging modalities; at last 30 papers were focused only on vitamin D.

bone metastases was introduced by Fuller Albright in 1941. In 1987 PTHrP was isolated confirming Albright's “humoral hypothesis” [20, 21]. The Parathyroid Hormone-Like Hormone (PTHrP) gene, which is located on the short arm of chromosome 12 encodes PTHrP. Alternative splicing gives rise in three separate isoforms of PTHrP of 139, 141, and 173 amino acids. PTHrP and PTH genes have quite comparable structures since the intron/exon organization of both genes encoding pre-pro sequences and the initial part portion of the mature peptides are identical. Furthermore, the amino-terminal end of secreted PTH and PTHrP are highly homologous, such that the first 13 amino acids are almost identical and there is

► **Table 1** Clinical features of hypercalcemia of malignancy.

Signs and symptoms of hypercalcemia of malignancy	
<b>Neurologic</b>	Muscle weakness, fatigue, hyporeflexia, apathy, disturbances of perception and behavior, lethargy, stupor, and coma
<b>Renal</b>	Polyuria, polydipsia, volume depletion, progressive renal insufficiency, nephrocalcinosis, and nephrolithiasis
<b>Gastrointestinal</b>	Nausea, anorexia, vomiting, constipation, ileus, peptic ulcer disease, pancreatitis
<b>Cardiovascular</b>	Shortened ST segments and QT intervals, widened T waves, and bundle branch block depressed ST segments, second-degree block, bradyarrhythmias, complete heart block, cardiac arrest, and hypertension
<b>Dermatologic</b>	Pruritus

► **Table 2** Mechanisms of hypercalcemia of malignancy.

Type	Incidence (%)	Bone Metastasis	Causal Agent
Humoral hypercalcemia	80	Minimal to Absent	PTHrP
Osteolytic hypercalcemia	20	Common and extensive	Cytokines, chemokines, PTHrP
1,25(OH) <sub>2</sub> D Lymphomas	< 1	Variable	1,25(OH) <sub>2</sub> D
Ectopic PTH production	< 1	Variable	PTH

PTHrP: Parathyroid hormone-related peptide; 1,25(OH)<sub>2</sub>D: 1,25-Dihydroxyvitamin D; PTH: Parathyroid hormone.

a similar secondary structure over the next 21 amino acids [22]. PTHrP regulates osteoblast, osteoclast, and chondrocyte differentiation, and is responsible for normal endochondral bone formation [22, 23], and is highly expressed in the placenta and the breast during lactation to transfer calcium to the fetus and regulates vascular smooth muscle, skin, hair follicles, hematopoiesis, teeth, and the development of brain [22, 24]. Despite their differences in protein structure, both PTH and PTHrP bind to a common receptor PTH1R activating similar second messengers such as cyclic adenosine monophosphate (cAMP), protein kinase A and C, phospholipase C, and inositol phosphate, so that PTHrP mimics the effects of PTH [5, 25, 26]. All the above intracellular messengers can trigger RANKL expression in osteoblasts, which in turn upon binding to the RANK receptor in osteoclasts lead to further osteoclast generation and activation.

Humoral hypercalcemia of malignancy accounts for approximately 80% of hypercalcemia in cancer patients [6, 26] and is commonly encountered in squamous cell carcinomas (head, lung and neck, esophageal, cervical, and colon cancers), breast, kidney, blad-

der, endometrial and ovarian cancers, and rarely in pancreatic neuroendocrine tumors [6, 27–31]. Hodgkin and non-Hodgkin lymphomas have also been reported to lead to PTHrP-related hypercalcemia of malignancy, albeit rarely [32, 33].

Although patients with Humoral Hypercalcemia of Malignancy (HHM) may manifest biochemical features compatible with PTH hypersecretion like increased bone resorption, increased calcium reabsorption in the ascending limb of loop of Henle and distal convoluted tubule, elevated excretion of nephrogenous cAMP, inhibition of phosphate reabsorption in the proximal convoluted tubule leading to hypophosphatemia and phosphaturia [17], studies conducted so far have failed to demonstrate native PTH secretion in patients with cancer, except those patients with parathyroid cancer [3, 34, 35]. It is well known that PTH also increases renal 1 $\alpha$ -hydroxylase activity leading to overproduction of 1,25(OH)<sub>2</sub>D, the active metabolite of vitamin D, in the proximal convoluted tubule increasing thus the intestinal absorption of calcium and phosphate [3, 34, 35]. Of note, PTHrP did not affect the 1 $\alpha$ -hydroxylase activity and the 1,25 (OH)<sub>2</sub>D production. Thus patients with primary hyperparathyroidism are characterized by elevated level of 1,25(OH)<sub>2</sub>D, while in patients with PTHrP-dependent HHM this increase is not seen [36]. This difference is probably attributed to the differences between PTH and PTHrP ligand receptor binding kinetics and activation of the downstream signaling pathways [37, 38]. PTHrP can activate the osteoclastic bone resorption and efflux of skeletal calcium and phosphate as PTH does, via increasing the expression of osteoblast receptor activator of nuclear factor  $\kappa$ B ligand (RANKL), which consequently activates the receptor activator of nuclear factor  $\kappa$ B (RANK) on the osteoclast precursors [38]. PTHrP, unlike PTH, uncouples bone resorption from formation by favoring osteoclast activation and osteoblast suppression and leading thus to marked calcium efflux from bone into circulation. This effect is in part mediated by cytokines such as tumor necrosis factor (TNF), prostaglandin-E, lymphotoxin, and interleukin-1 (IL-1) that stimulate osteoclasts and bone resorption [26].

#### Local osteolytic hypercalcemia with secretion of other humoral factors responsible for hypercalcemia

Osteolytic metastases, which lead to excessive calcium release from bone is responsible for approximately 20% of cases of hypercalcemia of malignancy [6]. The common causes of such metastases are multiple myeloma and metastatic breast cancer followed by leukemia and lymphoma [6, 39]. Local cytokines released from the tumor can stimulate the local production of PTHrP, which in turn induces RANKL/RANK interaction [40] resulting in excessive osteoclast activation, enhanced bone resorption and hypercalcemia [26, 41]. Interleukin-1 (IL-1), IL-3, IL-6, tumor necrosis factor  $\alpha$  (TNF $\alpha$ ), transforming growth factor  $\alpha$  and  $\beta$  (TGF $\alpha$ , TGF $\beta$ ), lymphotoxin, and prostaglandins E series are the main cytokines/humoral factors associated with increased bone remodeling and consequent hypercalcemia [39, 42]. A protein which plays important role in hypercalcemia associated with multiple myeloma is the macrophage inflammatory protein 1 $\alpha$  (MIP1 $\alpha$ ), which is known to induce osteoclastogenesis in human bone marrow cells and to inhibit the differentiation of marrow stromal cells into osteoblasts [43].

### Excess production of extra-renal 1,25-dihydroxyvitamin D

One percent (1%) of all cases of hypercalcemia of malignancy is due to increased ectopic production of the active metabolite of vitamin D by the tumor [6]. It is found to occur nearly exclusively in lymphomas (both Hodgkin and non-Hodgkin) while it has also been recognized in ovarian dysgerminoma [44, 45]. However, Shallis et al. (2018) [33] in single center retrospective study reported that the main mechanism by which non-Hodgkin lymphomas led to hypercalcemia was not mediated by active vitamin D or PTHrP, and remained unknown. Of note, hypercalcemia was found to be more prevalent in large diffuse B-cell lymphomas and in particular of the non-germinal cell subtype. Furthermore, the outcome was worse in patients with calcitriol-mediated hypercalcemia, indicating that calcitriol could serve as a marker of high-grade lymphoma or to its transformation [33].

Extra-renal 1,25-dihydroxyvitamin D production due to increased  $1\alpha$ -hydroxylase activity in tissues macrophages has been also reported in various nonmalignant granulomatous diseases such as sarcoidosis and other inflammatory conditions resulting in hypercalcemia [46]. It should be noted that under normal conditions, 25-hydroxyvitamin D is converted to the active vitamin D metabolite 1,25-dihydroxyvitamin D via the enzymatic activity of  $1\alpha$ -hydroxylase in the kidney, a process regulated by parathyroid hormone (PTH) [47]. However, in 1,25-dihydroxyvitamin D-induced hypercalcemia, the cancer cells recruit the adjacent macrophages and stimulate them to express  $1\alpha$ -hydroxylase with the result of the conversion of endogenous 25-hydroxyvitamin D into the active metabolite 1,25-dihydroxyvitamin D, which in turn binds to their receptors in the gut leading to an increased intestine calcium absorption and hypercalcemia (absorptive hypercalcemia) [17, 48].

### Ectopic secretion of parathyroid hormone (PTH)

Malignant cells [3, 34, 35] can also produce ectopic PTH accounting for less than 1% of cases of hypercalcemia of malignancy [6], which has been described in cases involving cancer of the lung and ovary, as well as sarcoma and neuroendocrine tumors [6, 17, 49–52]. However, primary hyperparathyroidism due to parathyroid adenoma or hyperplasia can also occur concomitantly in patients with malignancies [39, 53, 54]. Primary hyperparathyroidism as a result of parathyroid carcinoma has also been reported albeit extremely rare [55].

### Differential diagnostic approach

The investigation of hypercalcemia should begin with its underlying causes. Hypercalcemia develops in the context of known disease, which is the apparent cause, but sometimes there may be multiple causes. Although the symptoms and signs of hypercalcemia are similar, the clinical findings of the associated primary disorders are different and can be the key for differentiating the etiology of hypercalcemia. It should be noted that primary hyperparathyroidism and malignancy are the two main causes that comprise nearly 90% of hypercalcemia cases [5, 56, 57], so a diagnostic approach should first focus on distinguishing between these two entities. The natural history of both processes can help in establishing the diagnosis before purchasing laboratory tests. Among patients admitted to the hospital, hypercalcemia due to malignancy is 2–3 times more common than primary hyperparathyroidism while the source of malignancy often becomes evident from the history and

physical examination [5, 56]. For example, mild chronic hypercalcemia in an asymptomatic patient may suggest primary hyperparathyroidism. In contrast, patients with malignancy associated hypercalcemia often have rapidly increasing calcium concentrations along with a rapid duration of onset and are more likely to be symptomatic [5, 56].

The first step in the evaluation of the suspected hypercalcemia is the measurement of serum calcium. The most commonly determined is the total calcium, which includes both bound and unbound form. It is well known that calcium homeostasis is strongly affected by albumin concentration [58]; thus albumin levels must be measured for interpretation of the serum calcium; in case that albumin is abnormal, then serum calcium should be corrected taking into account the following formula:  $\text{calcium (mg/dl)} + 0.8 (4.0 - \text{patient's albumin level})$ . However, it should be noted that ionized calcium levels which can be measured directly, is the preferred method with the higher sensitivity, since albumin is the major but not the only carrier of calcium [3, 6]. After the laboratory confirmation of hypercalcemia, an initial panel of laboratory evaluation consisting of PTH, PTHrP, phosphorus, 25-hydroxyvitamin D, and 1,25-dihydroxyvitamin D should be obtained. ► **Table 3** summarizes the differential diagnosis of hypercalcemia of malignancy.

### Humoral hypercalcemia of malignancy

Elevated PTHrP with a decreased or low-normal serum PTH indicates humoral hypercalcemia of malignancy; if low-normal phosphorus and 1,25-dihydroxyvitamin D also exists, it confirms the diagnosis. Direct bone osteolysis is characterized by a low PTH, undetectable PTHrP and decreased 1,25-dihydroxyvitamin D with a high to normal phosphorus [59].

### Local osteolytic hypercalcemia

It is characterized by increased levels of phosphorus with suppressed PTH and low levels of 1,25(OH)<sub>2</sub>D (► **Table 3**). In case that hypercalcemia due to bone metastases is strongly suspected but not apparent, serum and urine protein electrophoresis, serum-free

► **Table 3** Laboratory findings for etiologies of hypercalcemia of malignancy.

Etiology	Humoral hypercalcemia	Osteolytic hypercalcemia	1,25(OH) <sub>2</sub> D mediated hypercalcemia
Calcium	High	High	High
Phosphorus	Low	High	High
PTH	Low	Low	Low
25(OH)D	Any value	Any value	Low or normal
1,25(OH) <sub>2</sub> D	Low or normal	Low or normal	High
PTHrP	High	Low	Low

PTHrP: Parathyroid hormone-related peptide; 1,25(OH)<sub>2</sub>D: 1,25 Dihydroxyvitamin D; PTH: Parathyroid hormone; 25(OH)D: 25 Hydroxyvitamin D.

light chains, and serum and urine immune fixation along with a skeletal radiographic images and/or bone scintigraphy should be performed for evaluation of a monoclonal gammopathy.

### Excess production of extra-renal 1,25-dihydroxyvitamin D

In cases of hypercalcemia caused by lymphoma, PTH is suppressed and serum 1,25-dihydroxyvitamin D is elevated without concomitant elevation of serum 25-hydroxyvitamin D.

### Ectopic secretion of parathyroid hormone (PTH)

It is important to note that patients with malignancies may exhibit a higher prevalence of primary hyperparathyroidism and in some cases, primary hyperparathyroidism is the sole cause of hypercalcemia in such patients [39, 53, 54, 60]; thus, given the fact that some cancers may produce PTH ectopically, whenever, in the setting of hypercalcemia, a high to normal PTH is measured suggesting the existence of parathyroid hyper-functioning, imaging tests

may be performed to evaluate the parathyroid glands for hyperfunction [39, 61].

Finally, a review of medications should be included during the evaluation of hypercalcemia [21, 39]; medications such as lithium, thiazide diuretics, and vitamin A and D supplements should be discontinued when possible. The above medications although may not entirely explain the hypercalcemia, they have the potential to make it worse or to unmask it.

### Management

The primary goal of therapy is the treatment of the underlying malignancy. The available pharmacologic treatments available are summarized in ► **Table 4**. The type and timing of therapy is determined by the severity of the hypercalcemia and associated symptoms; thus, in mild asymptomatic hypercalcemia, treatment could be delayed until the laboratory tests have been completed and a diagnosis has been made. However, in moderate to severe hypercalcemia, espe-

► **Table 4** Treatment of hypercalcemia of malignancy.

Agent	Regimen-Dosage	Onset of action	Duration of action	Practical considerations, SE	Approval Approval
<b>0.9% NaCl</b>	2–4 liter i. v./day	Immediate	2–3 days	Volume overload	
<b>Calcitonin</b>	4–8 units/kg SQ q 6–12 h	4–6 h	Up to 3 days	Tachyphylaxis develops after 72 h. SE: nausea, vomiting, and pain at the injection site	Approved by FDA for the treatment of hypercalcemic emergencies
<b>Bisphosphonates</b> <b>Zoledronic acid</b>	3–4 mg i. v. over 15–30 min	48 h	3–4 weeks	SE: Nephrotoxicity, infusion site reaction, bone pain and flu-like illness for the first 1 to 2 days after the infusion and osteonecrosis of the jaw. May repeat dosing after at least 7 days. Dose reduction according to creatinine clearance	Approved by FDA for the treatment of hypercalcemia of malignancy and the prevention of skeletal-related events in patients with bone metastases
<b>Pamidronate</b>	60–90 mg i. v. over 2–6 h	48 h	3–4 weeks	Do not use if glomerular filtration rate is less than 30 ml/min	Approved by FDA for the treatment of hypercalcemia of malignancy
<b>Corticosteroids</b>	200–400 mg hydrocortisone i. v./day for 3–5 days and then prednisone 10–20 mg/day for 7 days or prednisone 40–60 mg/day for 10 days	7 days	Unclear (perhaps 1 week)	More likely to benefit patients with 1,25(OH) <sub>2</sub> D syndrome from lymphoma than other malignancies. SE: hyperglycemia, hypertension, psychiatric disturbances, muscle weakness, peptic ulcer disease, and further immunosuppression	
<b>Denosumab</b>	120 mg SQ weekly for 4 weeks and monthly thereafter	7–10 days	3–4 months	Approved for hypercalcemia refractory to bisphosphonates therapy and the prevention of skeletal-related events in patients with solid tumors. SE include arthralgias, nausea, diarrhea, dyspnea, and osteonecrosis of the jaw	Approved by FDA for hypercalcemia refractory to bisphosphonates therapy and the prevention of skeletal-related events in patients with solid tumors
<b>Gallium Nitrate</b>	200 mg/m <sup>2</sup> per day for 5 days	4 days	2 weeks	SE: hypophosphatemia, anemia, and acute tubular necrosis	Approved by FDA for hypercalcemia of malignancy (but not available)
<b>Cinacalcet</b>	30 mg twice daily to 90 mg four times daily	2–16 weeks (titration phase)	80 weeks	Minimal SE include nausea, vomiting, diarrhea, myalgia, dizziness, hypertension	Approved by FDA for hypercalcemia of parathyroid carcinoma

SE: Side effects; FDA: Food and Drug Administration; SQ: Subcutaneous; i. v.: Intravenous; q: Every.

cially when it is followed by severe renal or neurologic symptoms, treatment should be started immediately. In patients with symptomatic severe hypercalcemia, therapy should be aimed specifically against the mediating mechanisms and it is essential to decrease serum calcium concentration, to increase urinary calcium excretion, and to inhibit bone resorption. Reducing intestinal calcium reabsorption is essential in patients with extra-renal 1,25-dihydroxyvitamin D production. Treatment is begun empirically at the time of presentation, while waiting several days for definitive serologic diagnosis. As many hypercalcemic patients are dehydrated at presentation, volume expansion with isotonic saline is the initial treatment of choice to restore renal perfusion and to increase renal calcium excretion [62]. The rate of hydration depends on the severity of hypercalcemia, the age of the patient and comorbidities like congestive heart failure, which may change the rate of isotonic saline infusion. Usually, 1–2 liter of isotonic saline bolus is administered followed by maintenance fluids at a rate of 100–150 ml/hour titrated to ensure a urine output of 100 ml/hour. In those patients with severe hypercalcemia and minimal comorbidities, 4–6 liters can be administered over the first 24 h. Just after normovolemia is established, either oral or maintenance i. v. fluids is continued to maintain satisfactory urine output until the anti-hypercalcemic agents start giving effect. The addition of furosemide to promote calciuresis is generally not recommended and should be reserved for patients with congestive heart failure and symptoms of volume overload or in case of oliguric renal failure [63].

Calcitonin is a rapid-acting peptide hormone secreted by the parafollicular C cells of the thyroid gland, which is a useful adjunctive initial therapy that inhibits osteoclastic bone resorption and renal calcium reabsorption [15, 64]. It is approved by Food and Drug administration (FDA) and when used with bisphosphonates, it can lower calcium level more rapidly than either agent alone. A disadvantage of calcitonin is the development of tachyphylaxis within approximately 3 days because of downregulation of the calcitonin receptors [48]. However, glucocorticoids can be used to enhance the effect of calcitonin by upregulating the cell surface calcitonin receptors and creating new ones on the osteoclast [41]. Calcitonin is usually administered at a dose of 4–8 IU/kg subcutaneously every 6–12 h; it begins to exert its effect within 4–6 h up to 72 h and decreases calcium levels by 1–2 mg/dl [5, 53, 62]. Side effects are minimal; nausea, vomiting, and injection site pain are the most common.

Bisphosphonates (BPs) are a class of pyrophosphate analogues that bind with high affinity to hydroxyapatite crystals in mineralized bone. They target osteoclasts inducing their apoptosis by inhibiting farnesyl pyrophosphate synthase, an enzyme that controls intracellular levels of several essential proteins for multiple biologic processes, resulting thus in the blockage of bone resorption [65]. They also affect proliferation and differentiation of osteoblasts preventing their apoptosis and they can also neutralize the RANKL-mediated stimulation of osteoclasts [18, 66, 67]. They are approved by FDA for treatment and prevention of osteoporosis, Paget's disease of bone, metastatic bone disease and they are effective in treating hypercalcemia of malignancy resulting in excessive bone resorption of any cause [68, 69]. The most commonly used nitrogen-containing (second generation) BPs are ibandronate, pamidronate, and zoledronic acid [68, 69]. BPs are first line therapy and should be given within 48 h of diagnosis, because it takes approximately 2–4

days for them to take effect with complete normalization of the corrected serum calcium level in 4–10 days [69, 70]. The preferred BPs for hypercalcemia of malignancy are the parenteral agent pamidronate (typical dose range is 60 mg to 90 mg, administered i. v. over 2–24 h with duration of achieved normocalcemia of 18 days) and zoledronic acid, the latter one is preferred, because it is more potent than the former one, is infused over 15 min and normocalcemia is maintained longer up to 32–43 days after infusion of 4 mg and 8 mg respectively [71]. Zoledronic acid, at a dose of 4 mg is approved in USA and the European Union for the treatment of hypercalcemia of malignancy and the prevention of skeletal-related events (SREs) in patients with bone metastases. Unfortunately, zoledronic acid has been associated with nephrotoxicity and the package insert recommend dose reduction according to creatinine clearance as follows: GFR > 60 ml/min: 4 mg, GFR 50–60 ml/min: 3.5 mg, GFR, 40–49 ml/min: 3.3 mg, GFR 30–39 ml/min: 3.0 mg and is not recommended if creatinine clearance is less than 30 ml/min. Ibandronate, with a dose range from 2 mg to 6 mg administered i. v., has been successfully used for the treatment of multiple myeloma patients with renal failure [72], but even though it is not indicated for the treatment of hypercalcemia of malignancy, it may offer an alternative therapy for patients with renal failure [73]. Side effects of BPs include nephrotoxicity, infusion site reaction, bone pain and flu-like illness during the first 1–2 days after the infusion and osteonecrosis of the jaw in patients receiving high-dose, with prolonged therapy and in those who have undergone dental procedures while on therapy [74].

Corticosteroids are most likely to have a clinical effect in the setting of the hypercalcemia associated with multiple myeloma and other hematological malignancies associated with 1, 25(OH)<sub>2</sub>D overproduction. In these situations, glucocorticoids inhibit 1 $\alpha$ -hydroxylase conversion of 25-hydroxyvitamin D into 1,25-dihydroxyvitamin D, therefore inhibiting intestinal calcium absorption. They also inhibit osteoclast resorption by decreasing tumor production of locally active cytokines in addition to having direct tumorolytic effects. Steroids are usually given as hydrocortisone 200–400 mg/day for 3–4 days and then prednisone 10–20 mg/day for 7 days or prednisone 40–60 mg/day for 10 days [21], with a decrease in serum calcium level up to > 3 mg/dl within 7 days after initiating therapy. When prednisone is not helpful following 10 days administration, it should be discontinued [18]. Clinicians should be aware that effects may not be apparent for more than 4 days and steroids should be used with caution because they may precipitate tumor lysis syndrome [75]. Side effects include hyperglycemia, hypertension, psychiatric disturbances, muscle weakness, peptic ulcer disease, and further immunosuppression [76].

Denosumab is a human monoclonal antibody to RANKL that inhibits osteoclasts activity and bone resorption [77]. It is approved by FDA for the treatment of osteoporosis and the prevention of skeletal-related events in patients with solid tumors [78]. In 2014, it was approved for hypercalcemia refractory to bisphosphonates therapy [79, 80]. Studies have shown that denosumab was more efficacious than zoledronic acid in delaying or preventing hypercalcemia of malignancy in patients with advanced cancer stages, including breast cancer, other solid tumors and multiple myeloma [79, 81]. It was given to patients with cancer and hypercalcemia refractory to i. v. bisphosphonates, defined as serum calcium



level > 12.5 mg/dl and who had received BPs within 7 days to 30 days. Denosumab dosed as 120 mg subcutaneously weekly for the first month and monthly thereafter lowered calcium level in 60 % of patients within 10 days and it had a median duration of 104 days [79]. Denosumab is not metabolized by the kidney, but the effect may be more pronounced in patients with renal failure, therefore dose reduction is recommended to avoid hypocalcemia [39, 82]. Side effects include arthralgias, nausea, diarrhea, dyspnea, osteonecrosis of the jaw (usually seen in patients treated with denosumab for at least several months), and hypocalcemia [83, 84].

Cinacalcet is a calcimimetic agent that activates the calcium sensing receptor (CaSR) on the surface of parathyroid glands. In addition to parathyroid cells, the CaSR is expressed along the nephron as well as in other tissues and is the regulator of PTH synthesis and secretion [85, 86]. By increasing the sensitivity of the CaSR to extracellular calcium it effects a reduction in PTH and therefore a reduction in serum calcium level [87, 88]. Cinacalcet has recently been approved by FDA for the treatment of hypercalcemia in patients with severe primary hyperparathyroidism (PHPT) when parathyroidectomy is contraindicated, those with parathyroid carcinoma, and finally for the treatment of patients with end stage renal disease on maintenance dialysis therapy and secondary hyperparathyroidism [26, 89]. To date two cases have been reported for hypercalcemia of malignancy treated with cinacalcet and it could be used as an additional effective therapeutic option, though not approved by FDA [26, 88, 90].

In patients with a contraindication to aggressive i. v. hydration and i. v. bisphosphonates, hemodialysis can be an effective treatment [6]. It is recommended for patients with a glomerular filtration rate of less than 10–20 ml/min, in patients already receiving hemodialysis or in patients with severe congestive heart failure and in cases of treatment failure or when calcium levels are markedly increased and are life threatening [91].

Gallium nitrate could be used in the treatment of hypercalcemia of malignancy via the inhibition of osteoclast activity and by increasing renal calcium excretion. It was administered as a slow i. v. infusion daily for 5 days and the typical dose used is 200 mg/m<sup>2</sup> [92]. It was well tolerated with side effect of hypophosphatemia, anemia and acute tubular necrosis [92]. However, it is no longer available for use since 2012, while the manufacturer discontinued its production.

## Conclusion

Hypercalcemia of malignancy is a common finding in patients with advanced stage cancers. It usually presents with markedly elevated calcium levels and patients are consequently severely symptomatic. Among the most common mechanisms which are responsible for the development of hypercalcemia of malignancy are the PTHrP-mediated humoral hypercalcemia, the osteolytic metastases-related hypercalcemia, the PTH-mediated hypercalcemia in patients with extra parathyroid cancers or parathyroid carcinoma, and the 1,25-dihydroxyvitamin D-mediated hypercalcemia. Diagnosis and differential diagnosis is made on the basis of the medical history of the patient and clinical examination, as well as the measurement of the aforementioned mediators of hypercalcemia. Treat-

ment includes i. v. hydration, calcitonin, bisphosphonates, denosumab, corticosteroids, and cinacalcet depending on the cause of hypercalcemia. Patients suffering from advanced underlying kidney disease and/or refractory severe hypercalcemia should be considered for hemodialysis. The administration of PTHrP-related antibodies has been recently emerged as a promising therapy for the management of HHM. Oncology and palliative care specialists should be involved early to guide the selection of cancer-targeted therapies and proposing potential comfort care options.

## Conflict of Interest

The authors declare that they have no conflict of interest.

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