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Editorial

Commentary on the endocrine society clinical practice guideline on the “treatment of hypercalcemia of malignancy in adults”☆

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1. Guidelines recommendations*

The Endocrine Society Guideline Writing Panel identified 8 questions that reflect common clinical scenarios encountered in treating HCM, for which the evidence was systematically assessed and recommendations derived [1].

1.1. Recommendation 1

In adults with HCM, we recommend treatment with IV BP or Dmab compared with management without an IV BP or Dmab. (1 ⊕ OOO).

1.2. Recommendation 2

In adults with HCM, we suggest treatment with Dmab over an IV BP. (2 ⊕ OOO).

1.3. Recommendation 3

In adults with severe HCM (serum calcium [SCa] > 14 mg/dl [3.5 mmol/l]), we suggest a combination of calcitonin and IV BP or Dmab as initial treatment compared with only IV BP or Dmab. (2 ⊕ OOO).

Abbreviations: CPG, Clinical Practice Guideline; Dmab, Denosumab; ES, Endocrine Society; EtD, Evidence-to-Decision; EMA, European Medicinal Agency; FDA, Food and Drug Administration; HHM, Humoral Hypercalcemia of Malignancy; HCM, Hypercalcemia of Malignancy; IV BP, Intravenous Bisphosphonate; LOH, Local Osteolytic Hypercalcemia; MM, Multiple Myeloma; RCTs, Randomized Controlled Trials; SCa, Serum Calcium; SRs, Systematic Reviews; SREs, Skeletal-Related Events; ZLN, Zoledronic Acid.

☆ Developer and Funding organization: Endocrine Society**Date of Release:** Dec 19, 2022 on lineMarch 2023 in print Volume 108, Issue 3, pages 507-528 https://doi.org/10.1210/clinem/dgac621**Target population:** Adults with hypercalcemia of malignancy**Stakeholders/health care settings:** Endocrinologists, oncologists, internists, family practitioners, emergency physicians, critical care and palliative care experts.Hospitals, outpatient facilities, and hospices**Cos-sponsoring organizations:** European Society of EndocrinologyAmerican Society of Bone and Mineral ResearchGuideline was shared pre-publication for public comments with members of Endocrine Society Guideline Writing Panel Members: Endocrine SocietyAmerican Society of Clinical OncologyGhada El-Hajj Fuleihan (Chair), Mathew T. Drake (Co-Chair), Gregory A. Clines, Mimi I. Hu, Claudio Marcocci, M. Hassan Murad, Thomas Piggott, Catherine Van Poznak, and Joy Y. Wu

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1.4. Recommendation 4

In adults with refractory/recurrent HCM on an IV BP, we suggest the use of Dmab compared with management without Dmab. (2 ⊕ OOO).

1.5. Recommendation 5

In adults with HCM from tumors associated with high calcitriol levels, such as lymphomas, who are already receiving glucocorticoid therapy but who continue to have severe or symptomatic hypercalcemia, we suggest the addition of an IV BP or Dmab compared with management without an IV BP or Dmab. (2 ⊕ OOO).

1.6. Recommendation 6

In adult patients with hypercalcemia due to parathyroid carcinoma, we suggest treatment with either a calcimimetic or an IV BP or Dmab. (2 ⊕ OOO).

1.7. Recommendation 7

In adult patients with hypercalcemia due to parathyroid carcinoma not adequately controlled despite treatment with a calcimimetic, we suggest the addition of an IV BP or Dmab compared with management without an IV BP or Dmab. (2 ⊕ OOO).

1.8. Recommendation 8

In adult patients with hypercalcemia due to parathyroid carcinoma who are not adequately controlled on an IV BP or Dmab therapy, we suggest the addition of a calcimimetic compared with management without a calcimimetic. (2 ⊕ OOO).

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The panel used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology to formulate the strength of recommendations (strong = 1, or weak = 2) and for grading the certainty of evidence (good, fair, low, very low), [2].

2. Background and framework for guideline development

Hypercalcemia of malignancy (HCM) [3] affects 2–30 % of patients with cancer and carries high morbidity and mortality [4–8]. HCM is most commonly associated with breast, lung, and renal cancers, and multiple myeloma. HCM pathophysiology includes humoral hypercalcemia of malignancy (HHM), local osteolytic hypercalcemia (LOH), hypercalcemia due to multiple myeloma, calcitriol-mediated hypercalcemia (such as due to lymphomas), and hypercalcemia due to parathyroid carcinoma. It presents with non-specific clinical manifestations related both to the severity of HCM and the rapidity with which calcium levels are reached [9]. Timely and efficacious therapies to control HCM are critical aspects of minimizing morbidity and time in-hospital

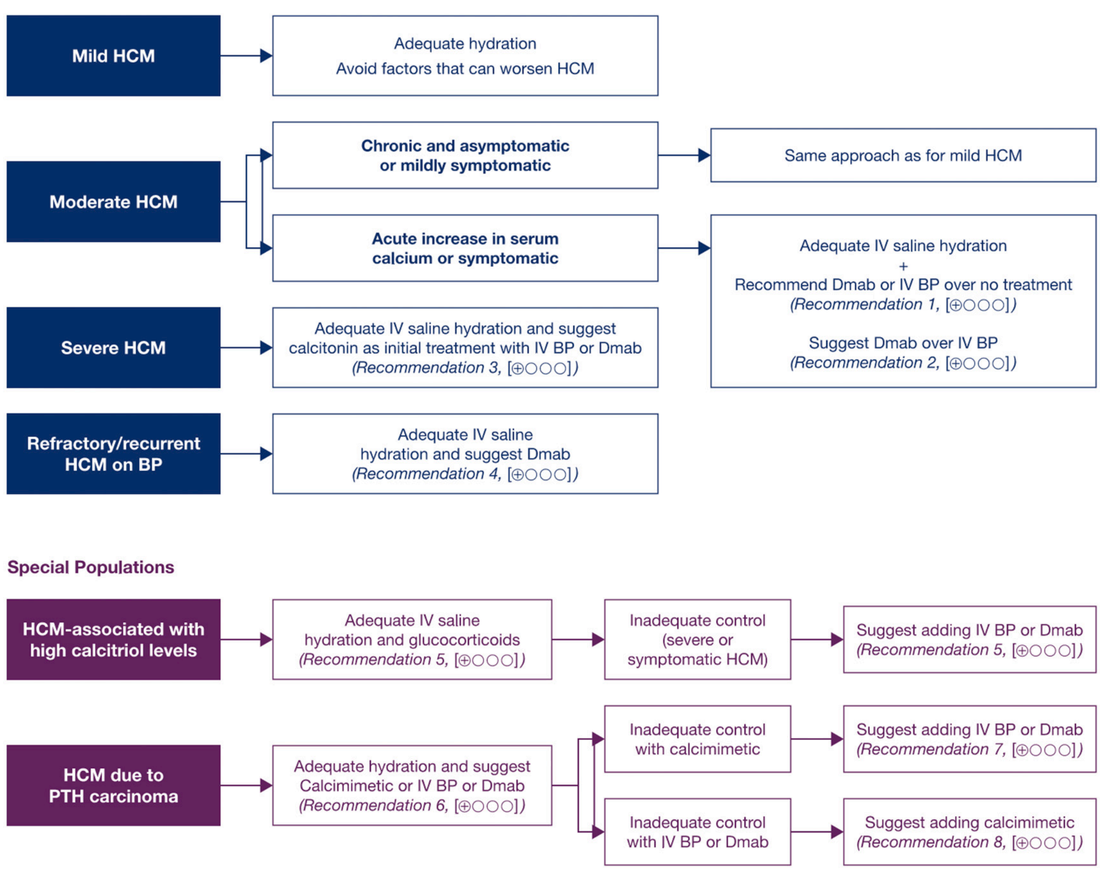

Fig. 1. Suggested workflow for the management of Hypercalcemia of Malignancy. Reproduced with permission from the Endocrine Society and Oxford University Press.
The therapeutic approach depends upon the pathophysiology and severity of hypercalcemia and the rapidity of serum calcium increase. The severity of hypercalcemia is classified as the following: mild, albumin-adjusted SCa < 12 mg/dl (14 mg/dl); (>3.5 mmol/l). Specific recommendations appear first in the manuscript. For full details regarding recommendations, and consideration encompassing evidence to decision framework domain, please refer to El-Hajj Fuleihan et al. [1], Seisa M et al. [15] and Bassatne A et al. [16]. Abbreviations: HCM, hypercalcemia of malignancy; IV, intravenous; Dmab, Denosumab; IV BP, intravenous bisphosphonate; SCa, serum calcium.

[10–13]. Therapies also allow opportunities for administration of anticancer treatments to improve survival and optimize quality of life.

The Endocrine Society (ES) gathered a multidisciplinary panel of clinical experts (endocrinology, oncology, primary care), and methodologists versed in evidence generation and appraisal and guideline development, to develop a Clinical Practice Guideline (CPG) and care pathway algorithm for the treatment of HCM in adults. The eight recommendations apply to adults with HCM due any of its known pathophysiologies and can be implemented in a hospital, hospice, or outpatient facility setting [1]. The guideline also provides a helpful workflow (Fig. 1) linking pathophysiology and characteristics of HCM (severity, recurrence and/or refractoriness) to each of the 8 recommendations. The guideline also provides essential information regarding therapies to be used (Table 1).

The guideline was developed in accordance with National Academy of Sciences recommendations for development of trustworthy guidelines [14], including careful vetting of potential conflicts of interest of guideline panel members. It was based on two (rather than the usual single) rigorous systematic reviews (SRs) [15,16]. The first evaluated evidence for each intervention benefits and harms [15], and the second evaluated other domains relevant to the Evidence-to-Decision (EtD) framework; contextual factors pertaining to patients and treating physicians (values, preferences, acceptability, feasibility, cost, cost-effectiveness, and equity), [1,16] to inform judgements and enable each recommendation. Five patient representatives with HCM from the US, Italy and Lebanon completed surveys that aided the guideline panel in prioritizing outcomes of interest. These included: survival, quality of life, HCM resolution, time to normocalcemia, duration of normocalcemia, ability to receive chemotherapy, decrease in skeletal-related events (SREs), and adverse events. Five comprehensive searches of several databases from each database's inception to April 6, 2022, any language, were conducted. The databases included Ovid MEDLINE, Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily; Ovid EMBASE; Ovid Cochrane Central Register of Controlled Trials; Ovid Cochrane Database of Systematic Reviews; and Scopus. The search strategy was designed and conducted by a medical reference librarian. The search reviewed 1949 citations, from which 21 studies were included. Additional references identified by the guideline panel members were reviewed for eligibility [15].

3. Evidence summary and appraisal

All, except for the first recommendation, were weak recommendations, with very low certainty of evidence. The panel noted that justification for a strong recommendation for recommendation 1 was based on GRADE guidance, namely when low-quality evidence (as described below) suggests benefit in a life-threatening situation [17,18]. Combined analyses from 4 studies demonstrated that HCM resolution was twice as likely in BP-treated patients compared to the placebo groups [15]. Pamidronate was shown to be less efficacious than zoledronic acid (ZLN) for the treatment of HCM in a double-blind RCT [19]. The systematic review did not identify any placebo-controlled trials with Dmab for the treatment of HCM, since such trial would have been unethical given earlier IV BP approval.

The SR did not identify any studies comparing BP versus Dmab in adults with HCM [15]. Recommendation 2 was therefore based on indirect evidence from studies conducted in patients with skeletal metastases, suggesting higher potency of Dmab versus BPs in preventing hypercalcemia development or its recurrence, and in reducing the incidence of skeletal related events [20–22].

Evidence for recommendation 3 was indirect and consisted of an observational retrospective study comparing serum calcium levels between patients with moderate to severe hypercalcemia who received calcitonin and IV BP [23] and a small case series in patients who received calcitonin with Dmab [24] compared to IV BP or Dmab alone. The first was non-revealing [23], whereas the small case series demonstrated that additional calcitonin therapy resulted in normocalcemia in two out of three patients [24]. In patients with severe HCM (and possibly in those with renal dysfunction), calcitonin therapy, limited to 24–48 h due to tachyphylaxis in addition to IV fluids, may be useful to temper hypercalcemia until IV BP or Dmab reaches maximum efficacy.

Evidence for recommendation 4 was indirect and consisted of a single arm study and 2 case series of patients with HCM refractory to IV BP who were subsequently treated with Dmab [10,24,25]. The studies revealed resolution of HCM and mortality reduction in patients with HCM refractory to IV BP subsequently treated with Dmab. The panel did not identify any evidence regarding patients with HCM refractory to Dmab subsequently treated with IV BP.

Evidence for recommendation 5 was indirect and consisted of 4 randomized controlled trials (RCTs) detailed under recommendation 1. Panel members underscored that IV BPs and Dmab are both effective antiresorptive drugs for inhibiting osteoclast-mediated bone resorption, that is expected to occur with calcitriol production. Evidence also included case reports of patients with lymphoma and calcitriol-mediated HCM treated with glucocorticoid therapy who were also treated with IV BP [26–28].

Evidence for recommendation 6 was indirect. It consisted of 2 RCTs using oral (rather than IV) BP in patients with primary hyperparathyroidism with negative results [29,30]; and of 3 observational studies using a calcimimetic that demonstrated resolution of HCM in one third of patients with intractable primary hyperparathyroidism or parathyroid carcinoma [31–33]. One case series and 8 case reports showed normalization of serum calcium in a subset of in patients with refractory HCM from PTH carcinoma who received denosumab [34–42].

Evidence for recommendation 7 was indirect and consisted of a retrospective study using Dmab in 8 patients with severe or symptomatic hypercalcemia due to primary hyperparathyroidism and 2 patients with parathyroid carcinoma. Five patients had previously received cinacalcet without response. All patients received Dmab, and normocalcemia was achieved in 4 patients [34].

Evidence for recommendation 8 was indirect and consisted of a modest effect of cinacalcet in two single arm studies in patients mostly with parathyroid carcinoma, most of whom had previously received BPs [32,33] and all of whom had undergone parathyroidectomy in one of the studies [32].

The most common adverse events noted in the SR included were fever, infusion site reactions, hypophosphatemia, hypocalcemia, nausea, diarrhea, and abnormal taste with BPs, and a higher incidence of grade 2 hypocalcemia in the Dmab-treated groups compared to the BP-treated groups. Calcimimetics caused nausea, vomiting and gastrointestinal side effects limiting dose escalation. Although the risk for osteonecrosis of the jaw and atypical femoral fractures with potent antiresorptive therapy is rare, it is further increased in patients with cancer and those treated with high-dose glucocorticoids.

The panel noted IV BPs (e.g., ZLN) requires resources (IV access; travel; and, in some countries, a nursing or hospital setting) and may worsen renal function. Dmab is easier to administer (subcutaneous administration) and can be given in outpatient setting, with less need to monitor renal function. However, institutions and regulatory bodies may limit its access. Calcimimetics are easily administered oral medications. Combination therapy would add to cost. Medication prices are likely to vary widely between countries, and feasibility would vary depending on country/region specific healthcare settings [16].

4. Limitations and gaps

As noted above, with the exception of the first recommendation, each recommendation included in the CPG was determined to be a weak recommendation with very low certainty of evidence. The guideline did not identify any direct evidence to support its recommendations. It relied on studies conducted in patients with skeletal metastases as a

Table 1
Treatment regimens for hypercalcemia of malignancy.

Intervention/dose frequency	Mode of action	Onset of action	Median duration of action/effect/proportion of subjects achieving normocalcemia	Adverse events/comments
Isotonic saline hydration/Bolus of 1-2 l then 200–500 ml/h to maintain urine output at 100–150 ml/h	Restores depleted intravascular volume. Enhances urinary calcium excretion	Immediate	• During infusion. • Lowers calcium by 1–1.5 mg/dl (0.25–0.375 mmol/l) over first 24 h	Carefully assess for volume overload
Loop diuretics[a]/Furosemide 160 mg/d to 100 mg/h intravenously, or 40–60 mg/d orally only to be administered after volume repletion	Increase urinary calcium excretion by inhibiting renal calcium reabsorption in the thick ascending loop of Henle, and proximal and distal renal tubules. Interferes with the chloride co-transport system	Within 3–60 min	• 2 h if bolus. • During therapy if IV drip. • Lowers calcium by 0.5–1.0 mg/dl (0.125–0.25 mmol/l) after resolution of volume depletion	Volume depletion, and worsening HCM. May be useful in patients at risk for volume overload/congestive heart failure
Salmon Calcitonin/CT 4–8 units/kg SQ every 6–12 h for 48–72 h	Inhibits bone resorption by interfering with osteoclast function. Promotes urinary calcium excretion, as well as that of magnesium, sodium, potassium and phosphate	4 to 6 h	• Intramuscular and SQ 6–8 h • Rapidly lowers calcium by 1–2 mg/dl (0.25–0.50 mmol/l)	Tachyphylaxis may occur after 48–72 h
Bisphosphonates/BPs	Pamidronate and zoledronic acid are nitrogen-containing BPs that inhibit bone resorption by inhibiting farnesyl pyrophosphate synthase (FPPS) within osteoclasts to cause osteoclast apoptosis. They also interfere with osteoclast recruitment and function			
Pamidronate/APD • 60–90 mg IV over 2–24 h. • Can be repeated every 2–3 wks		48 to 72 h	• 7–14 days; may last 2 to 4 wks. • Normalizes calcium in 60–70 % of patients	• Both APD and ZLN may cause kidney damage especially if glomerular filtration rate < 30–35 ml/min. • Acute-phase response relatively common; • hypocalcemia; renal insufficiency possible if decreased glomerular filtration rate; ONJ and atypical femoral fractures are very rare
Zoledronic acid/ZLN • 3–4 mg IV over 15–30 min. • Can be repeated in 7 days, if desirable calcium level not achieved, and every 3–4 wks thereafter		48 to 72 h	• 4–6 wks. • Normalizes calcium in 80–90 % of patients	Dose adjustment required if glomerular filtration rate < 60 ml/min, and administer over 60 min
Glucocorticoids • 200–400 mg hydrocortisone IV/day for 3–5 days. • 60 mg/day of prednisone for 10 days, or 10–20 mg/day for 7 days	Decrease intestinal calcium absorption. Inhibits 1α-hydroxylase and limits 1,25-dihydroxyvitamin D production by mononuclear cells in patients with granulomatous diseases or lymphoma	2 to 5 days	As long as on therapy	Hyperglycemia, altered mental status, and hypertension
Denosumab/Dmab • 120 mg SQ • Repeat 1, 2 and 4 wks later, then monthly thereafter	Inhibits bone resorption via inhibition of RANKL. Dmab is an antibody to RANKL. Upon binding to RANKL, Dmab blocks the interaction between RANKL and RANK (receptor on osteoclast surfaces) and prevents osteoclast formation and thus bone resorption	3 to 10 days	• Time to complete response 23 days. • Median duration of effect 104 days. • Normalizes calcium in at least 70 % of patients	• Acute-phase response rare; ONJ and atypical femoral fractures are rare. • Rebound osteoclastogenesis may occur with discontinuation. • Patients with GFR < 30 ml/min have a higher risk of hypocalcemia, and a lower dose should be considered
Calcimimetics Oral: Initial: 30 mg twice daily; increase dose incrementally every 2 to 4 wks (to 60 mg twice daily, 90 mg twice daily, and 90 mg 3 to 4 times daily) as necessary to normalize SCa levels	Calcium-sensing receptor agonist, reduces parathyroid hormone secretion, and may increase renal calcium absorption	2 to 3 days	• During therapy. • Reduces calcium by at least 1 mg/dl (0.25 mmol/l) in approximately 60 % of patients	• Nausea, vomiting, headache, and fractures. • Case reports indicate reduction of calcium levels in patients with refractory HCM related to non–small-cell lung, neuroendocrine, breast, or renal cancer

Source: Information on mode of action, onset of action and duration of effect obtained in part from Lexicomp© Copyright 1978–2021, or relevant papers cited from Chakhtoura M, El-Hajj Fuleihan G. *Endocrinol Metab Clin North Am,* 2021; 50 [4]: 781–792 [12] and Guise T and Wysolmerski J. *N Engl J Med,* 2002;386:1443–1451. [13].

Abbreviations: HCM, hypercalcemia of malignancy; IV, intravenous; ONJ, osteonecrosis of the jaw; RANK, receptor activator of nuclear factor kappa-B; RANKL, receptor activator of nuclear factor kappa-B ligand; SQ, subcutaneous.

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[a] Loop diuretics should not be used routinely. However, in patients with renal insufficiency or heart failure, judicious use of loop diuretics may be required to prevent fluid overload during saline hydration.

surrogate for HCM, and with intractable hyperparathyroidism as substitute for parathyroid carcinoma. It also relied on surrogate outcomes that consisted of prevention of metastases and prevention of hypercalcemia as substitutes for pre-selected outcomes relevant to the treatment of HCM. For studies of potent antiresorptive agents (IV BPs versus Dmab), this reflects the absence of direct head-to-head RCTs in patients with HCM. Likewise, in patients with calcitriol dependent HCM there exists no direct evidence to address the impact of pharmacologic intervention with antiresorptive therapy (IV BP or Dmab) to inform treatment recommendations. The same also applies to the treatment of HCM due to parathyroid carcinoma with regards to initial selection of drug therapy and/or the use of combination therapy.

Regulatory approval of ZLN was based on 2 pivotal studies that compared it to pamidronate and included fewer than 300 subjects [43]. The FDA has approved Dmab for the treatment of HCM refractory to BP therapy based on positive results from an open-label, single-arm study of patients with advanced cancer and persistent HCM despite BP treatment [44,45]. It is not approved by the EMA for the treatment of HCM. Cinacalcet approval for the management of HCM in parathyroid carcinoma is based on a single arm dose-titrating study of 29 patients described in the CPG [32,46].

5. Research agenda and future directions

Overall, the dearth of high-quality data relevant to the optimal pharmacologic treatment of patients with HCM was disappointing to the guideline committee and pointed to a clear need to obtain high quality data in future RCTs designed with endpoints relevant to both care providers and patients.

Direct head-to-head studies of IV BP versus Dmab in patients with HCM are needed to guide treatment decisions in this population. Given the comparative rarity of HCM, these are likely to require multi-site and/or multi-national approaches to achieve clinically relevant outcomes. In addition to biochemical indices and standard medically determined measures of effectiveness, additional important endpoints to be studied should include comparative costs/cost-effectiveness of treatments, patient values and preferences for therapy, acceptability/feasibility of each therapy, equity of therapy, and the ability to deliver healthcare services.

Additional clinically important issues related to the optimal use of antiresorptive therapy in patients with HCM which require careful study include 1) determining the optimal sequence of IV BP versus Dmab (and vice versa); 2) establishing an approach to limit the well-recognized rebound hypercalcemia that occurs following Dmab discontinuation; 3) clarifying the optimal use of glucocorticoids (including both dose and duration, and relationship to concomitant use of anti-resorptive therapy) in patients with calcitriol-mediated HCM; and 4) determining the optimal use of calcimimetic agents in combination with anti-resorptive therapies in patients with HCM from unresectable parathyroid carcinoma.

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