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Clinical Practice Guideline

Treatment of Hypercalcemia of Malignancy in Adults: An Endocrine Society Clinical Practice Guideline

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Abstract

Background: Hypercalcemia of malignancy (HCM) is the most common metabolic complication of malignancies, but its incidence may be declining due to potent chemotherapeutic agents. The high mortality associated with HCM has declined markedly due to the introduction of increasingly effective chemotherapeutic drugs. Despite the widespread availability of efficacious medications to treat HCM, evidence-based recommendations to manage this debilitating condition are lacking.

Objective: To develop guidelines for the treatment of adults with HCM.

Methods: A multidisciplinary panel of clinical experts, together with experts in systematic literature review, identified and prioritized 8 clinical questions related to the treatment of HCM in adult patients. The systematic reviews (SRs) queried electronic databases for studies relevant to the selected questions. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology was used to assess the certainty of evidence and make recommendations. An independent SR was conducted in parallel to assess patients' and physicians' values and preferences, costs, resources needed, acceptability, feasibility, equity, and other domains relevant to the Evidence-to-Decision framework as well as to enable judgements and recommendations.

Results: The panel recommends (strong recommendation) in adults with HCM treatment with denosumab (Dmab) or an intravenous (IV) bisphosphonate (BP). The following recommendations were based on low certainty of the evidence. The panel suggests (conditional recommendation) (1) in adults with HCM, the use of Dmab rather than an IV BP; (2) in adults with severe HCM, a combination of calcitonin and an IV BP or Dmab therapy as initial treatment; and (3) in adults with refractory/recurrent HCM despite treatment with BP, the use of Dmab. The panel suggests (conditional recommendation) the addition of an IV BP or Dmab in adult patients with hypercalcemia due to tumors associated with high calcitriol levels who are already receiving glucocorticoid therapy but continue to have severe or symptomatic HCM. The panel suggests (conditional recommendation) in adult patients with hypercalcemia due to parathyroid carcinoma, treatment with either a calcimimetic or an antiresorptive (IV BP or Dmab). The panel judges the treatments as probably accessible and feasible for most recommendations but noted variability in costs, resources required, and their impact on equity.

Conclusions: The panel's recommendations are based on currently available evidence considering the most important outcomes in HCM to patients and key stakeholders. Treatment of the primary malignancy is instrumental for controlling hypercalcemia and preventing its recurrence. The recommendations provide a framework for the medical management of adults with HCM and incorporate important decisional and contextual factors. The guidelines underscore current knowledge gaps that can be used to establish future research agendas.

Key Words: hypercalcemia of malignancy, antiresorptive therapy, bisphosphonate, denosumab, refractory, calcitonin, calcimimetics, GRADE methodology, Evidence-to-Decision framework, knowledge gaps, clinical practice guidelines

Abbreviations: BP, bisphosphonate; CGC, Clinical Guidelines Committee; CPG, clinical practice guideline; Dmab, denosumab; EtD, evidence to decision; FDA, U.S. Food and Drug Administration; GDP, Guideline Development Panel; GI, gastrointestinal; GRADE, Grading of Recommendations Assessment, Development and Evaluation; GRADEpro GDT, GRADEpro Guideline Development Tool; HCM, hypercalcemia of malignancy; IV, intravenous; ONJ, osteonecrosis of the jaw; QOL, quality of life; RANK, receptor activator of nuclear factor κ-B; RANKL, RANK ligand; RCT, randomized clinical trial; SCa, serum calcium; SR, systematic review; SRE, skeletal-related event; UGPS, ungraded good practice statement.

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List of Recommendations

Adults With Hypercalcemia of Malignancy

Question 1. Should a bisphosphonate or denosumab vs no treatment with a bisphosphonate or denosumab be used for adults with hypercalcemia of malignancy?

Recommendation 1

In adults with hypercalcemia of malignancy (HCM), we recommend treatment with an intravenous (IV) bisphosphonate (BP) or denosumab (Dmab) compared with management without an intravenous (IV) bisphosphonate (BP) or denosumab (Dmab). (1⊕OOO)

Question 2. Should denosumab vs a bisphosphonate be used for adults with hypercalcemia of malignancy?

Recommendation 2

In adults with hypercalcemia of malignancy (HCM), we suggest treatment with denosumab (Dmab) over an intravenous (IV) bisphosphonate (BP). (2⊕OOO)

Question 3. Should addition of calcitonin vs no calcitonin be used for adults with severe hypercalcemia of malignancy who will be started on a bisphosphonate or denosumab?

Recommendation 3

In adults with severe hypercalcemia of malignancy (HCM) (serum calcium [SCa] > 14 mg/dL [3.5 mmol/L]), we suggest a combination of calcitonin and an intravenous (IV) bisphosphonate (BP) or denosumab (Dmab) as initial treatment compared with only intravenous (IV) bisphosphonate (BP) or denosumab (Dmab). (2⊕OOO)

Remark Calcitonin treatment should be limited to 48 to 72 hours due to tachyphylaxis.

Refractory and Recurrent Hypercalcemia

Question 4. Should denosumab vs no denosumab be used for adults with refractory/recurrent hypercalcemia of malignancy on a bisphosphonate?

Recommendation 4

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

Hypercalcemia Due to Calcitriol-Associated Malignancy

Question 5. Should a bisphosphonate or denosumab vs no bisphosphonate or denosumab be used for adults with hypercalcemia resulting from tumors associated with high calcitriol levels who are already treated with a glucocorticoid?

Recommendation 5

In adults with hypercalcemia of malignancy (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 intravenous (IV) bisphosphonate (BP) or denosumab (Dmab) compared with management without an intravenous (IV) bisphosphonate (BP) or denosumab (Dmab). (2⊕OOO)

Adults With Hypercalcemia Due to Parathyroid Carcinoma

Question 6. Should a calcimimetic vs a bisphosphonate or denosumab be used for adults with hypercalcemia due to parathyroid carcinoma?

Recommendation 6

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

Remarks

- In adult patients with parathyroid carcinoma, surgery should be considered when feasible, once control of severe hypercalcemia has been achieved; however, surgical considerations were outside of the scope of this guideline.
- Depending on the clinical situation and severity of hypercalcemia, an IV BP or Dmab may be useful prior to calcimimetic initiation. In adults with mild hypercalcemia and related symptoms, we suggest starting therapy with calcimimetics; conversely, for adults with moderate to severe hypercalcemia and related symptoms, an IV BP or Dmab should be the initial therapy.
- This recommendation considers the more rapid onset of action of an IV BP or Dmab, and generally better tolerability profile than a calcimimetic (as adverse events are common with increasing calcimimetic doses).

Question 7. Should addition of a bisphosphonate or denosumab vs no addition of a bisphosphonate or denosumab be used for adults with hypercalcemia due to parathyroid carcinoma in patients not adequately controlled with a calcimimetic?

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 intravenous (IV) bisphosphonate (BP) or denosumab (Dmab) compared with management without an IV BP or Dmab. (2⊕OOO)

Question 8. Should a calcimimetic vs no calcimimetic be used for adults with hypercalcemia due to parathyroid carcinoma who are not adequately controlled with a bisphosphonate or denosumab?

Recommendation 8

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

Introduction

Hypercalcemia of malignancy (HCM), a condition associated with high morbidity and mortality, is the most common metabolic complication of malignancies (1). It is estimated to affect between 2% and 30% of patients with cancer, with rates that vary depending on cancer type and disease stage (1–5). The most common cancers associated with HCM are solid tumors, such as breast, lung, and renal cancer, and multiple myeloma (6). The clinical manifestations of HCM are nonspecific, and symptoms are closely related to the severity of HCM, the rapidity with which calcium levels were reached (7), and/or the presence of bone metastasis. The severity of HCM can be defined as mild (serum calcium [SCa] < 12 mg/dL [3 mmol/L]), moderate (SCa 12-14 mg/dL [3-3.5 mmol/L]), or severe (SCa >14 mg/dL [3.5 mmol/L]). An alternative definition of hypercalcemia severity is provided by the National Cancer Institute's Common Terminology Criteria for Adverse Events (see Appendix A).

Mild hypercalcemia may cause fatigue, constipation, and cognitive dysfunction. In addition to the symptoms seen at milder levels of hypercalcemia, higher SCa levels and/or rapidly increasing SCa levels above the normal range can cause polyuria, polydipsia, and renal failure and may be associated with reduced quality of life (QOL), poor prognosis, and increased hospitalization rates and mortality (8–10). Although early series had reported 30-day mortality rates of 50% in patients with HCM (11), these estimates have improved markedly over the past several decades, primarily because of the advent of more effective antineoplastic and supportive measures, including antiresorptive agents. Treatment of the primary malignancy is instrumental in controlling hypercalcemia and preventing its recurrence.

In addition to treatment of the underlying malignancy, therapeutic interventions for HCM are based on correction of hypovolemia, enhancing renal calcium excretion with fluids and occasionally loop diuretics, and decreasing bone resorption with antiresorptive drugs (12, 13). Fluid hydration constitutes the earliest treatment due to the rapidity of therapeutic effect, sometimes with the addition of furosemide. There is very little evidence to support the efficacy and safety of the use of furosemide in the management of HCM (14). Additional therapeutic options include calcitonin because of its rapid onset of action, in combination with more potent antiresorptive agents, such as bisphosphonates (BPs) administered intravenously or denosumab (Dmab). Alternative therapeutic strategies may combine antiresorptive agents with glucocorticoids in HCM caused by elevated calcitriol levels or calcimimetics in HCM due to parathyroid carcinoma or ectopic parathyroid hormone secretion (7).

The Endocrine Society gathered a multidisciplinary panel of clinical experts, together with experts in systematic literature review, to develop a clinical practice guideline (CPG) for the treatment of HCM. This CPG will apply to the treatment of adult patients with HCM in a hospital, outpatient, or hospice setting and when HCM is due to any of the following pathophysiologies: humoral HCM, local osteolytic HCM, hypercalcemia due to multiple myeloma, calcitriol-mediated hypercalcemia (such as occurs with lymphoma), or hypercalcemia due to parathyroid carcinoma. The recommendations are framed by the pathophysiology of the HCM. Although this CPG was developed by endocrinologists, oncologists, and primary care physicians (specialties represented within the writing group), they are broadly applicable to all providers who care for patients with HCM. Patients and their families are important stakeholders, and their perspective was taken into account in this CPG when proceeding from the evidence to the recommendations. Please see Table 1 below for details regarding dosing, onset of action, and frequency of use for drugs discussed in this guideline (15, 16).

The group prioritized 8 clinical questions related to the treatment of HCM and identified important outcomes of interest. Survival, QOL, resolution of HCM, and time to normocalcemia were deemed critical outcomes; duration of normocalcemia, ability to receive chemotherapy, and decrease in skeletal-related events (SREs) were deemed important. Adverse events (such as hypocalcemia, renal failure, acute phase reaction, bone pain, osteonecrosis of the jaw (ONJ), and gastrointestinal [GI] symptoms) were deemed important or nonimportant, depending on the specific recommendation. The panel conducted interviews with 5 patients diagnosed with HCM due to different etiologies, and who received their treatments in different countries worldwide (17). Patients consistently placed a high value on treatment of HCM with regards to survival, QOL, and resolution of HCM, but varied in prioritization of other prespecified outcomes of interest, such as adverse events, SREs, and ability to receive chemotherapy. This variability may be partially explained by differences in disease prognosis between patients (17). Each recommendation was based on a systematic review (SR) that queried electronic databases for studies relevant to that question (18). The Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology was used to assess the certainty of evidence for making the specific recommendations. An SR was also conducted in parallel to assess patient and physician values and preferences and other domains relevant to the Evidence-to-Decision (EtD) framework, including medication costs (17). The SRs did not identify any studies providing information comparing the resources required, costs, and cost-effectiveness for the various interventions. A survey conducted with experts from countries in Asia, the Middle East, Europe, and North America revealed wide variability in cost incurred from IV BPs, Dmab, and to a lesser extent from calcimimetics worldwide (17).

Adults With Hypercalcemia of Malignancy

Background

The estimated median length of stay associated with admission for HCM in the United States as determined from a nationwide database of almost 5000 individuals was 4 days, with reported in-hospital mortality of 6.8% (19). When compared with historical values, this shorter mean length of stay may also reflect the now-common use of potent antiresorptive medications administered to a large proportion of patients (30 to 40%) in this more recent series to manage HCM and

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 to 2 L then 200 to 500 mL/hour to maintain urine output at 100 to 150 mL/hour.	Restores depleted intravascular volume. Enhances urinary calcium excretion.	Immediate	During infusion. Lowers calcium by 1 to 1.5 mg/dL (0.25 to 0.375 mmol/L) over first 24 hours.	Carefully assess for volume overload.
Loop diuretics*/ Furosemide 160 mg/d to 100 mg/h intravenously, or 40 to 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 cotransport system.	Within 3 to 60 minutes	2 hours if bolus. During therapy if IV drip. Lowers calcium by 0.5 to 1.0 mg/dL (0.125 to 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 to 8 units/kg Intramuscular or SQ every 6 to 12 hours for 48 to 72 hours.	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 hours	6 to 8 hours. Rapidly lowers calcium by 1 to 2 mg/dL (0.25 to 0.50 mmol/L).	Tachyphylaxis may occur after 48 to 72 hours.
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 to 90 mg IV over 2 to 24 hours. Can be repeated every 2 to 3 weeks.		48 to 72 hours	7 to 14 days; may last 2 to 4 weeks. Normalizes calcium in 60% to 70% of patients.	May cause kidney damage especially if glomerular filtration rate <30 to 35 mL/ minute. Acute-phase response relatively common; hypocalcemia; renal insufficiency possible if decreased glomerular filtration rate; Atypical femoral fractures are rare and ONJ occurs infrequently.
Zoledronic acid/ZLN 3 to 4 mg IV over 15 to 30 minutes. Can be repeated in 7 days, if desirable calcium level not achieved, and every 3 to 4 weeks thereafter.		48 to 72 hours	4 to 6 weeks. Normalizes calcium in 80% to 90% of patients.	May cause kidney damage especially if glomerular filtration rate <30 to 35 mL/ minute. Dose adjustment required if glomerular filtration rate <60 mL/min, and administer over 30 to 60 minutes.
Glucocorticoids 200 to 400 mg hydrocortisone IV/day for 3 to 5 days. 60 mg/day of prednisone for 10 days, or 10 to 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 weeks 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	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; Atypical femoral fractures are rare and ONJ occurs infrequently. Rebound osteoclastogenesis may occur with

(*continued*)

Table 1. Continued

Intervention/dose frequency	Mode of action	Onset of action	Median duration of action/ effect/proportion of subjects achieving normocalcemia	Adverse events/comments
	osteoclast surfaces) and prevents osteoclast formation and thus bone resorption.			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 weeks (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 decrease renal calcium reabsorption.	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 (15) and Guise T and Wysolmerski J. *N Engl J Med*, 2002;386:1443-1451. (16).
Abbreviations: HCM, hypercalcemia of malignancy; IV, intravenous; ONJ, osteonecrosis of the jaw; RANK, receptor activator of nuclear factor κ-B; RANKL, receptor activator of nuclear factor κ-B ligand; SQ, subcutaneous.
*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.

its comorbid complications. Timely and efficacious therapies to control HCM are critical aspects of minimizing morbidity and time hospitalized (20–22).

A substantial proportion of cases are due to parathyroid hormone–related peptide, which enhances osteoclast differentiation and function (1, 16, 23). Osteoclasts mediate bone resorption and, therefore, skeletal calcium release into the systemic circulation. This is a purely humoral mechanism that occurs in the absence of bone metastases. Osteoclast formation is dependent on the receptor activator of nuclear factor κ-B (RANK)–RANK ligand (RANKL) system (24). There are 2 forms of antiresorptive therapies available that reduce osteoclast activity (see Fig. 1).

Dmab, a humanized monoclonal antibody to RANKL, prevents osteoclast formation from pre-osteoclasts. In contrast, BPs target mature osteoclasts to induce osteoclast apoptosis (see Fig. 1). The pivotal trials that led to the regulatory approval for the use of these medications in HCM were exclusively placebo controlled. To date, no clinical studies have directly compared the effectiveness of BPs vs Dmab for the treatment of adults with HCM. Rebound HCM has been associated with Dmab discontinuation in patients with metastatic malignancies (25–27).

In addition to the specific recommendations outlined below and in the suggested workflow (see Fig. 2), the panel judged the following ungraded good practice statements (UGPSs) as integral to the care of all adult patients with HCM (see Table 2).

Question 1. Should a bisphosphonate or denosumab vs no treatment with a bisphosphonate or denosumab be used for adults with hypercalcemia of malignancy?

Recommendation 1

In adults with hypercalcemia of malignancy (HCM), we recommend treatment with an intravenous (IV) bisphosphonate (BP) or denosumab (Dmab) compared with management without an intravenous (IV) bisphosphonate (BP) or denosumab (Dmab). (1⊕OOO)

Summary of Evidence

The evidence summaries, meta-analysis results, and a detailed summary of the evidence and EtD tables can be found online at https://guidelines.gradepro.org/profile/MRIMrEG_9fk.

Benefits and Harms

Four published studies were identified that examined the efficacy of BP therapy compared with placebo for the treatment of HCM (18). Of note, these studies only included a few outcomes of interest. The BPs evaluated were etidronate (2 studies), clodronate, and pamidronate. The study of Rotstein et al specifically enrolled patients with breast cancer, whereas the other 3 studies enrolled patients with HCM due to any type of cancer (30). In combined analyses from the 4 studies, 61.3% of patients treated with a BP experienced resolution of HCM compared with 27.5% of patients in the placebo groups (rate ratio [RR] 2.22; 95% CI 1.57 to 3.14). In the 4 evaluated studies, all patients received the standard care of that time, which included IV fluid hydration to enhance renal perfusion and induce calciuria. As a result of IV hydration, significant declines in SCa values were also observed in the placebo groups, albeit not to the degree observed with additional pharmacologic BP treatment.

Singer et al also reported increased mortality in patients treated with BP, but this difference was not statistically significant (RR 1.52; 95% CI 0.91 to 2.53) (31). Adverse events were more common with BP treatment (RR 2.33; 95% CI 1.16 to 4.69). The most common adverse events were fever, infusion site reactions, hypophosphatemia, hypocalcemia, nausea, diarrhea, and abnormal taste.

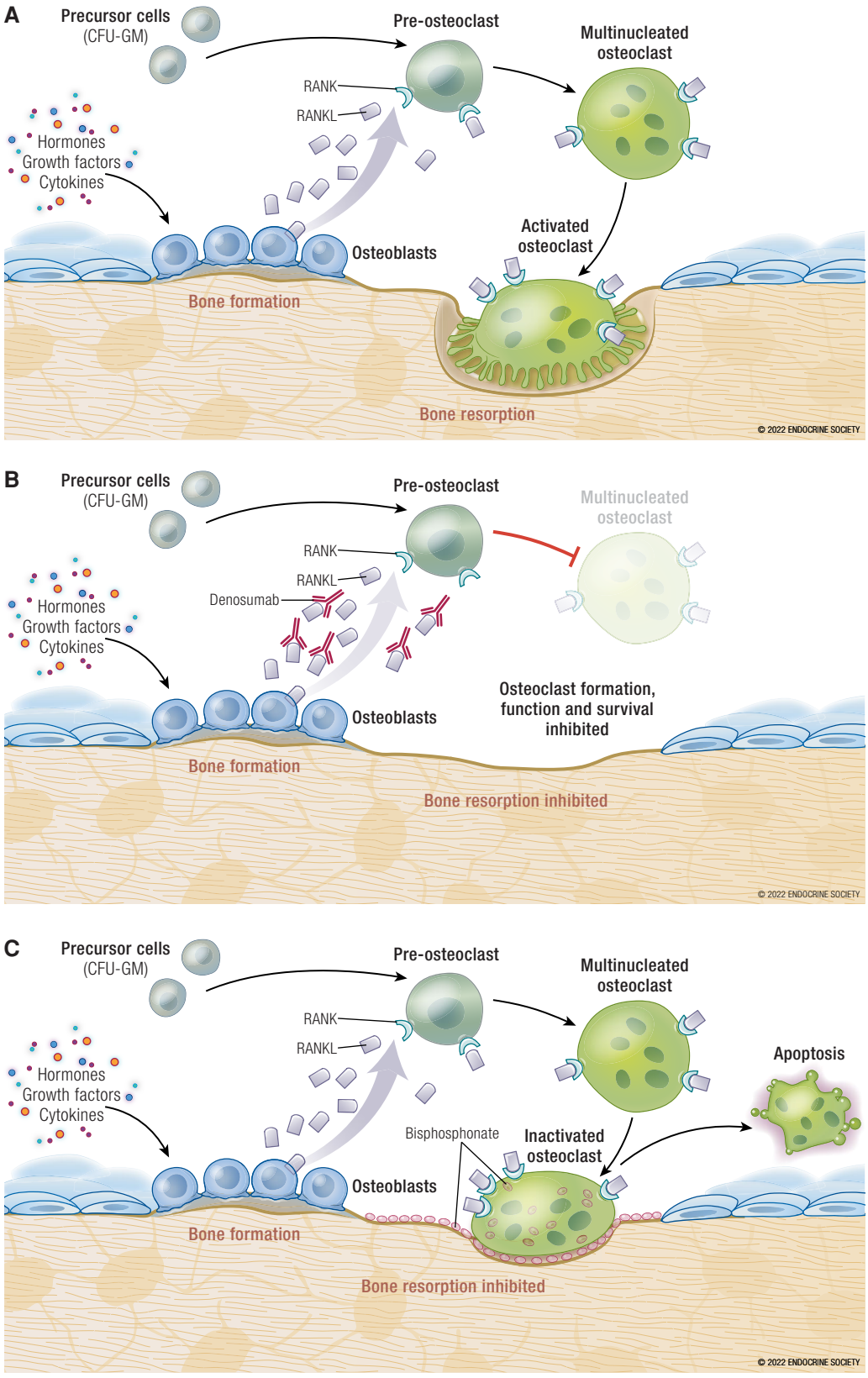

Figure 1. Osteoclast formation, activity, and pharmacologic inhibition. (A) Osteoclasts develop from osteoclast precursor cells when receptor activator of nuclear factor κ B (RANK) ligand (RANKL), produced by osteoblasts, binds to the receptor RANK on pre-osteoclasts. Multinucleated osteoclasts adhere to bone where they undergo differentiation into mature activated osteoclasts which resorb bone. (B) Denosumab is a humanized monoclonal antibody that binds to RANKL to block RANK:RANKL binding, resulting in inhibition of osteoclast formation, function, and survival. (C) Bisphosphonates adhere to the mineral component of bone. During the resorptive process, mature osteoclasts endocytose bisphosphonates, resulting in osteoclast inactivation and apoptosis. Abbreviation: CFU-GM, colony forming unit granulocyte–macrophage. Adapted from Boyle WJ, Simonet WS, Lacey DI. *Nature*. 2003;423(6937):337-342. (24)

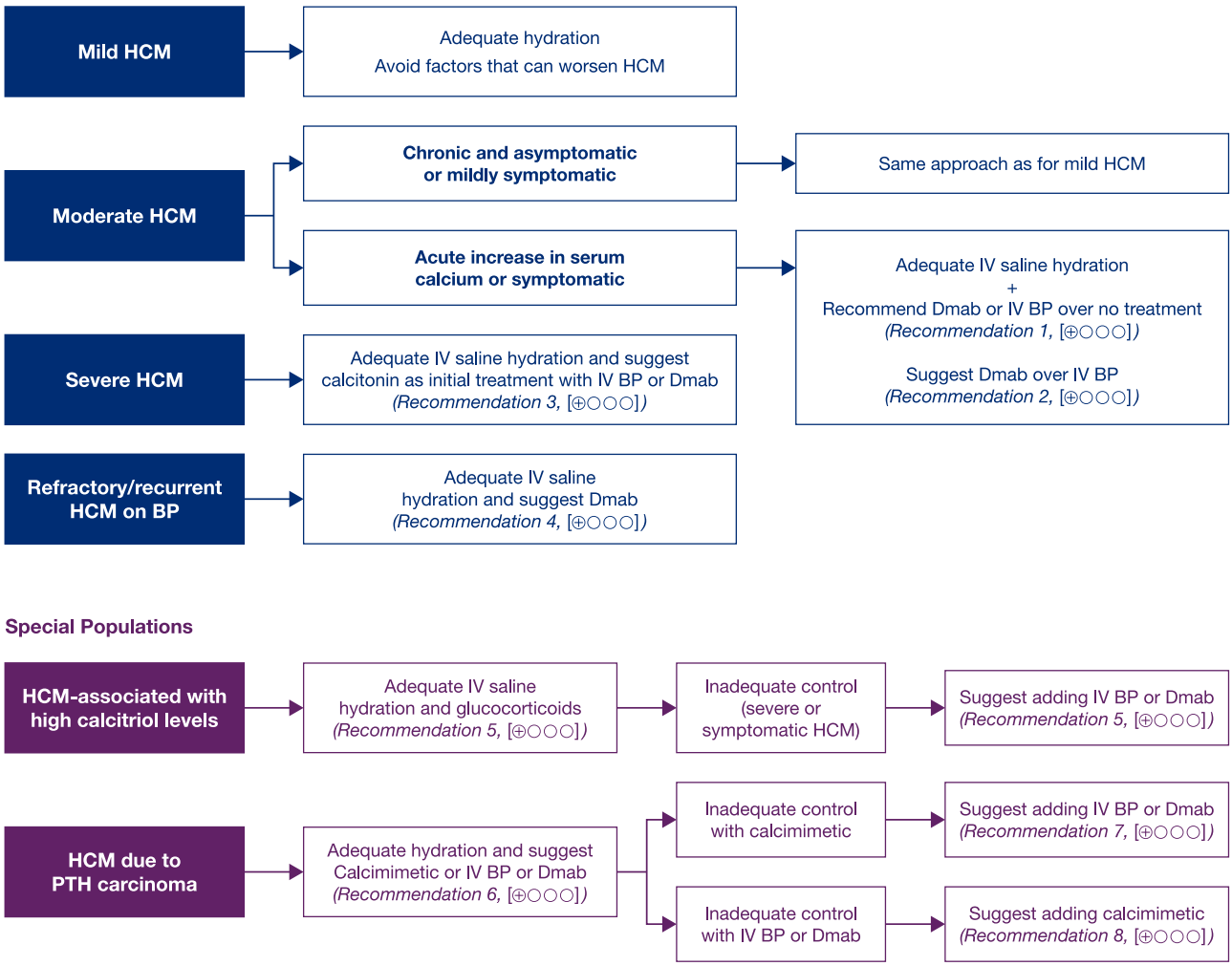

Figure 2. Suggested workflow for the management of HCM. The therapeutic approach depends upon the pathophysiology and severity of hypercalcemia and the rapidity of serum calcium increase. The severity of hypercalcemia is classified as the following: mild, albumin-adjusted SCa < 12 mg/dL (<3 mmol/L); moderate, albumin-adjusted SCa 12 to 14 mg/dL (3 to 3.5 mmol/L; Severe, albumin-adjusted SCa > 14 mg/dL; (>3.5 mmol/L). The ungraded good practice statements are listed below (see Table 2) and various recommendations are detailed in the main text. *Refer to the full EtDs and recommendations for additional considerations behind the recommendations. Abbreviations: HCM, hypercalcemia of malignancy; IV, intravenous; Dmab, Denosumab; IV BP, intravenous bisphosphonate; SCa, serum calcium.

Other Evidence-to-Decision Criteria and Considerations

An obvious consideration in the evaluation of the 4 reported studies is that 3 of them used early BPs (etidronate and clodronate) that do not contain a nitrogen moiety and are therefore substantially less potent than more recently developed nitrogen-containing BPs such as pamidronate. Furthermore, neither etidronate nor clodronate is approved by the U.S. Food and Drug Administration (FDA) or by regulatory bodies in other countries for the treatment of HCM. In contrast, pamidronate is approved worldwide for the treatment of HCM.

Consideration given to studies outside of the review criteria identified other agents, including the nitrogen-containing BPs ibandronate and zoledronic acid, and Dmab. A randomized clinical trial (RCT) in patients with HCM compared IV ibandronate to pamidronate and demonstrated that ibandronate had similar efficacy to pamidronate (32). However, ibandronate is not FDA approved for the management of HCM. Pamidronate was shown to be less efficacious than zoledronic acid for the treatment of HCM in a double-blind RCT in which the response rate was higher and duration was longer with zoledronic acid (33). In a study in which patients with breast cancer metastatic to bone were randomized to zoledronic acid or placebo and followed for SREs, HCM occurred in 2.6% of participants treated with zoledronic acid vs 8.8% of patients treated with placebo (34). Zoledronic acid is approved by the FDA for the treatment of HCM and is a commonly used drug for this indication.

Unlike BPs, no placebo-controlled trials have been reported with Dmab for the treatment of HCM since the implementation of such a trial would have been unethical given the availability of BPs. However, Dmab has been compared with BPs where it has demonstrated a delay in HCM development and reduced the risk of recurrent HCM (35, 36). Dmab has been approved by the FDA for HCM refractory to BP therapy. In terms of acceptability and feasibility, Dmab is easier to administer (subcutaneous administration) with less need to monitor renal function, in mild and moderate renal failure, or in chronic kidney disease stages 1 to 4. However, some institutions and regulatory bodies may limit access to Dmab, which can, in turn, limit its use. The panel noted IV BPs may worsen renal function; in that context, Dmab would be favored in patients

Table 2. Ungraded good practice statements

Ungraded good practice statement (UGPS) definition: Necessary actionable and clear guideline statements that are supported only by overwhelming indirect evidence. The supporting direct evidence is either unavailable or considered inappropriate for a systematic review process. UGPS should describe the population and intervention options and, if appropriate, comparator components of the recommendation (28, 29).

The panel reviewed the criteria for UGPSs and makes the following UGPSs for patients with HCM:

UGPS 1: In adults with HCM, adequate hydration with intravenous (IV) fluids is first-line therapy while awaiting the effect of antiresorptive drugs. Therapy should be tailored according to cardiac function.

UGPS 2: In adults with HCM, dental hygiene and oral health, including visual examination of the mouth, should be monitored in the context of the provision of antiresorptive therapy.

UGPS 3: To avoid hypocalcemia in adults with HCM who receive antiresorptive therapy, vitamin D levels should be monitored and managed in accordance with Endocrine Society vitamin D guidelines. These guidelines are however not specific to patients with HCM.

UGPS 4: In adults with HCM, renal function (creatinine clearance or estimated glomerular filtration rate [eGFR]) should be assessed prior to administration of IV BPs.

UGPS 5: In adults with HCM and renal insufficiency (defined as creatinine clearance <60 mL/min) who are treated with IV BPs, administer renal BP dosing of zoledronic acid over 30 to 60 minutes or renal BP dosing of pamidronate over 2 to 24 hours.

UGPS 6: In adults with HCM, serum magnesium and phosphorous levels should be monitored and repleted if determined to be low.

UGPS 7: In adults with HCM, clinical oncology consultation for treatment of the underlying malignancy should be undertaken.

UGPS 8: In adults with hypercalcemia due to parathyroid carcinoma, surgical consultation should be pursued for definitive treatment.

with HCM and underlying renal insufficiency (see Appendix B). Hypocalcemia eczema, and infections such as cellulitis have been reported with Dmab treatment (37). Atypical femoral fractures are rare and ONJ occur infrequently.

In addition to common adverse effects of IV BPs (eg, fever, infusion site reaction, hypocalcemia, hypophosphatemia), the panel noted undesirable effects of treatment including renal failure (specific to IV BPs) or drug withdrawal–associated bone loss or fracture (specific to Dmab).

Justification for the Recommendation

The panel notes that justification for a strong recommendation came from GRADE guidance (38, 39) when low-quality evidence suggests benefit in a life-threatening situation (evidence regarding harms can be low or high); see Table 3. The panel discussed that HCM is often a life-threatening situation and noted that this consideration justifies the strong recommendation.

The panel concluded that the balance of effects probably favors the intervention. It was anticipated that resources, cost-effectiveness, and equity would likely vary, but the treatment would probably be feasible and accessible (see Appendix B).

Question 2. Should denosumab vs a bisphosphonate be used for adults with hypercalcemia of malignancy?

Recommendation 2

In adults with hypercalcemia of malignancy (HCM), we suggest treatment with denosumab (Dmab) over an intravenous (IV) bisphosphonate (BP). (2⊕OOO)

Table 3. GRADE strength of recommendation classifications and interpretation

Strength of recommendation	Criteria	Interpretation by patients	Interpretation by health care providers	Interpretation by policy makers
1. Strong recommendation for or against	Desirable consequences CLEARLY OUTWEIGH the undesirable consequences in most settings (or vice versa).	Most individuals in this situation would want the recommended course of action, and only a small proportion would not.	Most individuals should follow the recommended course of action. Formal decision aids are not likely to be needed to help individual patients make decisions consistent with their values and preferences.	The recommendation can be adopted as policy in most situations. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.
2. Conditional recommendation for or against	Desirable consequences PROBABLY OUTWEIGH undesirable consequences in most settings (or vice versa).	The majority of individuals in this situation would want the suggested course of action, but many would not.	Clinicians should recognize that different choices will be appropriate for each individual and that clinicians must help each individual arrive at a management decision consistent with the individual's values and preferences. Decision aids may be useful in helping patients make decisions consistent with their individual risks, values and preferences.	Policy-making will require substantial debate and involvement of various stakeholders. Performance measures should assess whether decision making is appropriate.

Data from Schünemann HJ, et al. *Blood Adv*. 2018, Nov 27;2(22):3198-3225 (40).

Summary of Evidence

The evidence summaries, meta-analysis results, and a detailed summary of the evidence and EtD tables can be found online at https://guidelines.gradepro.org/profile/J36s7Ht14Zg.

Benefits and Harms

The SR did not identify any prospective studies evaluating adult patients with HCM treated with either a BP or Dmab with the resolution of HCM evaluated as an endpoint (18).

The SR identified 5 prospective phase 3 clinical trials that enrolled patients with solid tumors and evidence of bone metastases or multiple myeloma in which patients were randomized to treatment with either monthly zoledronic acid (4 mg dose) or Dmab (120 mg dose). One study evaluated overall survival (41). Three studies evaluated the time to first SRE defined as pathologic fracture, radiation or surgery to bone, or spinal cord compression (35, 42, 43). Only 1 study evaluated the prevention of HCM as the primary endpoint (36). None of these studies can be considered as direct evidence to evaluate whether a BP or Dmab is more effective for the treatment of HCM. However, the panel noted that Stopeck et al found that the incidence of HCM was lower in Dmab-treated patients (1.7%) compared with those treated with zoledronic acid (3.5%) (35). Diel et al reported that Dmab delayed the time to first on-study HCM compared with zoledronic acid (hazard ratio [HR] 0.63%; 95% CI 0.41 to 0.98; $P = .042$). Dmab also reduced the risk of recurrent HCM by 52% (RR 0.48, 95% CI 0.29 to 0.81, $P = .006$) (36). Additionally, the panel noted that Dmab was associated with fewer SREs (HR from 2 studies was 0.83 [0.77, 0.89]) (35, 42) but also with more hypocalcemic events than zoledronic acid. Bone turnover markers were also lower with Dmab than with zoledronic acid (35, 42). Collectively, findings from these 5 studies suggest that Dmab is associated with greater suppression of bone turnover when compared with zoledronic acid, which is expected to be translated into a more favorable impact in patients with HCM. However, the panel wished to emphasize that each of the included studies neither required nor assessed for baseline HCM prior to study entry. Finally, overall survival was not different between the 2 treatment groups in any of the studies. Thus, based on very low certainty of evidence, Dmab over IV BP is suggested as a treatment for adults with HCM.

There is 1 retrospective study recently published evaluating the response of HCM to either Dmab (n = 18) or IV BP (n = 22) in multiple myeloma patients who had a corrected SCa > 10.5 mg/dL (2.625 mmol/L) (44). The authors showed no difference in the primary endpoint of complete response (defined as corrected SCa < 10.5 mg/dL [2.625 mmol/L]) by day 7 with 89% and 86% in the Dmab and BP-treated patients, respectively. The rate of recurrent HCM was 12% in the Dmab group and 29% in the BP group ($P = .257$). There was no statistically significant difference in rates of hypocalcemia, although there was a slightly higher incidence of grade 2 hypocalcemia in the Dmab-treated group than in the BP-treated group.

The panel noted that the outcome of hypocalcemia was deemed not important in the outcome prioritization process. However, clinicians should be vigilant for the risk of hypocalcemia in any patient receiving antiresorptive therapy, especially in the setting of vitamin D deficiency or renal insufficiency.

Other Evidence-to-Decision Criteria and Considerations

The panel conducted a SR and did not identify any evidence for equity, resources required, or cost-effectiveness in the context of HCM. The panel considered the desirable effects were small, and there was no evidence identified for important and critical undesirable effects. Refer to "Other Evidence-to-Decision Criteria and Considerations" in Question 1 regarding acceptability and feasibility, adverse effects with IV BPs, and undesirable effects of treatment, including renal failure that might also be relevant to Question 2.

Justification for the Recommendation

The panel based its recommendation on very low certainty evidence demonstrating lower incidence of SREs and increased rates of hypocalcemia, both implying higher potency, with Dmab as compared with a BP.

The panel, therefore, concluded that the balance of effects probably favors the intervention and that resources, cost-effectiveness, and equity would all vary, but that the treatment would probably be feasible and accessible (see Appendix B).

Question 3. Should addition of calcitonin vs no calcitonin be used for adults with severe hypercalcemia of malignancy who will be started on a bisphosphonate or denosumab?

Recommendation 3

In adults with severe hypercalcemia of malignancy (HCM) (serum calcium [SCa] > 14 mg/dL [3.5 mmol/L]), we suggest a combination of calcitonin and an intravenous (IV) bisphosphonate (BP) or denosumab (Dmab) as initial treatment compared with only intravenous (IV) bisphosphonate (BP) or denosumab (Dmab). (2⊕OOO)

Remark

Calcitonin treatment should be limited to 48 to 72 hours due to tachyphylaxis.

Summary of Evidence

The evidence summaries, meta-analysis results, and a detailed summary of the evidence and EtD tables can be found online at https://guidelines.gradepro.org/profile/3ojG_3nY8_M.

Benefits and Harms

The SR identified 1 retrospective comparative analysis of 140 patients treated with a BP and/or calcitonin for the treatment of moderate to severe HCM (corrected SCa > 13 mg/dL [3.25 mmol/L] or ionized calcium >1.50 mmol/L [0.375 mmol/L]) (18, 45). Despite higher initial SCa levels in the combination than in the BP-only group, SCa levels at 24, 48, and 72 hours were similar. Resolution of HCM occurred in 69 of 94 patients who received an IV BP, and in 28 of 46 patients who received both an IV BP and calcitonin (RR 1.21; 95% CI 0.93 to 1.57). Mortality was lower in the BP-only group (RR 0.45; 95% CI 0.22 to 0.91). Adverse events (hypocalcemia) were reported in 5 of 94 patients who received an IV BP and in 1 of 46 patients

who received both an IV BP and calcitonin (incident rate ratio 0.49; 95% CI 0.14-1.69). A case series reported on 4 patients with HCM due to multiple myeloma who had renal dysfunction and were treated with Dmab. Three of the 4 patients also received calcitonin. SCa normalized in 2 of these patients (46).

Other Evidence-to-Decision Criteria and Considerations

The panel conducted a SR and did not identify any evidence for acceptability, equity, resources, or feasibility. The panel expressed concern with increased mortality in the calcitonin plus BP group in the identified study. It was noted that these findings may reflect chance, or that the combination group had more severe illness, as communicated by the manuscript authors. Given this uncertainty, the panel judged "don't know" for the balance of effects. The panel noted that changes in medication cost have made calcitonin extremely expensive in the United States.

Justification for the Recommendation

The panel made their recommendation based on the limited evidence provided in the only study identified. The panel discussed that, in patients with severe HCM and possibly in those with renal dysfunction, calcitonin in addition to IV fluids to temper the hypercalcemia (while awaiting the effects of the more potent antiresorptive agents BPs or Dmab), may be considered.

The panel, therefore, concluded that the balance of effects was unknown and that the treatment cost is moderate, thus equity would vary, but that the treatment would probably be feasible and accessible (see Appendix B).

Research Considerations for Recommendations 1 to 3

Considerations for future research include:

- RCTs with BPs and/or Dmab in patients with HCM are needed to provide stronger evidence to guide drug selection in this vulnerable population.
- Head to head RCTs to assess clinically important outcomes are needed.
- RCTs may require global collaboration because of the relative rarity of HCM.
- Significant gaps in research exist regarding complementary evidence relevant to the treatment of HCM including health services delivery, costs/cost-effectiveness of treatment, patients' values and preferences, equity, acceptability, and feasibility.
- Evidence regarding the pathophysiology and management of rebound HCM following Dmab therapy discontinuation is needed.

It was noted that there may be ethical concerns related to equipoise. However, the current uncertainty should be addressed by the research community in an ethical manner, which might include assessment in patients with moderate HCM in whom equipoise may be more justifiable.

Refractory and Recurrent Hypercalcemia

Background

Treatments with IV fluids, calcitonin, and IV BPs or Dmab can be highly effective in managing patients with HCM. For the majority of these patients, IV BPs are often the standard therapy implemented for patients with moderate–severe or symptomatic HCM. Unfortunately, some patients will develop short-interval recurrences or become refractory to IV BP therapy, typically in the setting of progressive cancer.

Both IV BPs and Dmab have shown efficacy in the management of HCM (42, 47, 48). The treatment of HCM refractory to IV BP therapy was investigated in an open-label, phase 2 study of Dmab (49). In this study, Dmab was shown to be efficacious for lowering SCa levels to the target range within 10 days, with a median duration of response of 104 days. Treatment of HCM comparing the sequence of an IV BP followed by Dmab vs Dmab followed by an IV BP has not been studied.

Question 4. Should denosumab vs no denosumab be used for adults with refractory/recurrent hypercalcemia of malignancy on a bisphosphonate?

Recommendation 4

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

Summary of Evidence

The evidence summaries, meta-analysis results, and a detailed summary of the evidence and EtD tables can be found online at https://guidelines.gradepro.org/profile/zzboJM2x61E.

Benefits and Harms

The SR identified 3 publications that reported on 44 patients and indirectly address the question of sequencing Dmab after IV BP for HCM management (18). Each study was single arm. One was a phase 2 study, while the other 2 publications were case series (46, 49, 50). Collectively, these data provide evidence for the ability of Dmab to lower SCa levels in patients with HCM following BP exposure. Toxicities from Dmab therapy in these studies included hypocalcemia and hypophosphatemia.

The guideline panel made its recommendation by assessing indirect evidence from single-armed studies of patients with HCM refractory to IV BP who were then subsequently treated with Dmab. The panel identified as important both resolution of HCM and a reduction in mortality in patients with HCM refractory to IV BP who then received Dmab treatment. The panel did not identify any evidence relevant to patients who had HCM refractory to Dmab who were treated subsequently with an IV BP.

Other Evidence-to-Decision Criteria and Considerations

This recommendation is focused on treating HCM that warrants hospitalization. Factors that impacted the EtD include the lack of rigorous clinical trials examining the sequencing of therapy and the financial consideration that Dmab is reimbursed as an outpatient medication but is less commonly reimbursed when used during hospitalization. Refer to "Other Evidence-to-Decision Criteria and Considerations" in Question 1 regarding acceptability and feasibility, adverse effects with IV BPs, and undesirable effects of treatment, including renal failure that might also be relevant to Question 4.

Justification for the Recommendations

The guideline panel made its recommendation by assessing indirect evidence from single-armed studies on patients with HCM refractory to IV BP who were subsequently treated with Dmab. The panel identified as important both resolution of HCM and a reduction in mortality in patients with HCM refractory to IV BP who then received Dmab treatment. No studies of HCM in patients refractory to Dmab therapy who then received IV BP were identified. The panel noted that evidence demonstrating resolution of refractory/recurrent HCM with IV BP followed by Dmab, but not for the comparator, was identified. The panel also noted that, in the United States, Dmab is FDA approved for HCM following IV BP treatment only. The panel concluded that the balance of effects was unknown and resources required, cost-effectiveness, and equity all varied, but that the treatment would probably be feasible and accessible (see Appendix B).

Research Considerations

Considerations for future research include:

- RCTs are needed to assess the order of administering an IV BP followed by Dmab and vice versa.
- Such studies should examine the efficacy of the intervention, cost-effectiveness, and patient-reported outcomes.

Hypercalcemia Due to Calcitriol-Associated Malignancy

Background

Ectopic production of the active form of vitamin D, 1,25-dihydroxyvitamin D (or calcitriol), is a less common mechanism of HCM that is almost exclusively seen with lymphomas. Calcitriol-induced HCM leads to increased calcium and phosphorus absorption from the GI tract and to increased osteoclast-mediated bone resorption. A retrospective study of patients with non-Hodgkin lymphoma with HCM found that progression-free survival was worse with elevated calcitriol levels, a possible surrogate marker for more advanced disease (51). Glucocorticoids interfere with GI calcium absorption (52) and are also useful in this context due to their ability to inhibit the 1-α-hydroxylase enzyme, thereby limiting the conversion of precursor 25-hydroxyvitamin D to calcitriol (53, 54). Restriction of dietary calcium intake is also required. Often patients with calcitriol–mediated HCM will have continued hypercalcemia despite glucocorticoid treatment.

Question 5. Should a bisphosphonate or denosumab vs no bisphosphonate or denosumab be used for adults with hypercalcemia resulting from tumors associated with high calcitriol levels who are already treated with a glucocorticoid?

Recommendation 5

In adults with hypercalcemia of malignancy (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 intravenous (IV) bisphosphonate (BP) or denosumab (Dmab) compared with management without an intravenous (IV) bisphosphonate (BP) or denosumab (Dmab). (2⊕OOO)

Summary of Evidence

The evidence summaries, meta-analysis results, and a detailed summary of the evidence and EtD tables can be found online at https://guidelines.gradepro.org/profile/eS0pSwpzm3c.

Benefits and Harms

The SR did not identify any direct evidence evaluating the use of a BP or Dmab in patients with calcitriol-mediated HCM who were already receiving glucocorticoid therapy but who continued to have severe or symptomatic HCM (18). It identified 4 prospective, randomized, placebo-controlled studies that included patients with HCM who responded to IV BP therapy (RR 2.22; 95% CI: 1.57 to 3.14) (30, 31, 55, 56).

However, given the serious indirectness of the evidence identified, the panel drew upon case reports from the literature that reported on patients with lymphoma and calcitriol-mediated HCM treated with glucocorticoid therapy who were also treated with an IV BP (57–59). Due to the indirectness of the evidence, the panel judged by voting that it was not possible to determine how substantial the desirable effects of the addition of an IV BP or Dmab to glucocorticoid therapy are in patients with calcitriol-mediated HCM.

Other Evidence-to-Decision Criteria and Considerations

The panel conducted a SR and did not identify any evidence for the balance of effects, resources required, cost-effectiveness, or equity. Refer to "Other Evidence-to-Decision Criteria and Considerations" in Question 1 regarding acceptability and feasibility, adverse effects with IV BPs, and undesirable effects of treatment, including renal failure that might also be relevant to Question 5. With both antiresorptive therapies, although the risk for ONJ and of atypical femoral fractures is low, it is further increased in patients treated with high-dose glucocorticoids.

Justification for the Recommendations

IV BPs and Dmab are both effective antiresorptive medications for inhibiting the osteoclast-mediated bone resorption that occurs with excessive calcitriol production. The panel concluded that the balance of effects, resources required, cost-

effectiveness, and equity all varied, but that the treatment would probably be feasible and accessible (see Appendix B).

Research Considerations

Considerations for future research include:

- Head to head RCTs of IV BPs vs Dmab are needed to assess clinically important outcomes for this intervention, including clinical improvement.
- Because of the rarity of this condition, RCTs may require global collaboration.
- Assessing appropriate glucocorticoid dosing and duration in this population and determining continued glucocorticoid need if antiresorptive therapy is administered are needed.
- Significant gaps in research exist regarding complementary evidence for the treatment of HCM, including health services delivery, costs/cost-effectiveness of treatment, patients' values and preferences, equity, acceptability, and feasibility.

Adults With Hypercalcemia Due to Parathyroid Carcinoma

Background

Parathyroid carcinoma is a rare disease, accounting for less than 1% of all cases of primary hyperparathyroidism (60). Clinical manifestations are characterized by symptoms of hypercalcemia that are usually moderate to severe at diagnosis. Surgical removal of parathyroid carcinoma should be considered if feasible, but surgical intervention is beyond the scope of this guideline. Parathyroidectomy may not be possible in some cases. Furthermore, local or distant recurrence, usually heralded by a progressive increase of SCa level, may occur in more than 50% of cases. Thus, medical management of HCM is frequently required.

Cinacalcet has been approved by the U.S. FDA (61) and by the European Medical Agency (62) for the treatment of HCM in adult patients with parathyroid carcinoma. Cinacalcet is effective in lowering SCa levels, but adverse events, mainly GI, may prevent the use of a fully effective dose (60). The IV BP zoledronic acid is approved worldwide for the management of HCM, and Dmab is also approved in many countries for this same indication (15).

Question 6. Should a calcimimetic vs a bisphosphonate or denosumab be used for adults with hypercalcemia due to parathyroid carcinoma?

Recommendation 6

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

Remarks

- In adult patients with parathyroid carcinoma, surgery should be considered when feasible, once control of severe HCM has been achieved; however, surgical considerations were outside of the scope of this guideline.
- Depending on the clinical situation and severity of hypercalcemia, an IV BP or Dmab may be useful prior to calcimimetic initiation. In adults with mild HCM and related symptoms, we suggest starting therapy with calcimimetics; conversely, for adults with moderate to severe HCM and related symptoms, an IV BP or Dmab should be the initial therapy.
- This recommendation considers the more rapid onset of action of an IV BP or Dmab, and generally better tolerability profile than a calcimimetic (as adverse events are common with increasing calcimimetic doses).

Summary of Evidence

The evidence summaries, meta-analysis results, and a detailed summary of the evidence and EtD tables can be found online at https://guidelines.gradepro.org/profile/VGI38boz-F8.

Benefits and Harms

The SR identified 5 studies that provided indirect evidence to address this question (18, 63–67). Two RCTs comparing the oral BP alendronate vs placebo in patients with primary hyperparathyroidism (63, 65) did not demonstrate a significant difference in the resolution of hypercalcemia (odds ratio 1.13; 95% CI 0.07 to 18.75). In 3 observational studies in patients with intractable primary hyperparathyroidism or parathyroid carcinoma (64, 66, 67), SCa levels normalized in 14 of 43 patients treated with cinacalcet. In 1 case series and 9 case reports that included a total of 19 patients (11 of whom had parathyroid carcinoma) with HCM refractory to cinacalcet and/or BPs, 11 patients (8 with parathyroid carcinoma) had resolution of their HCM after Dmab treatment. Durable resolution of HCM, ranging from 2 to 14 months, was reported in 5 patients (68–76). With respect to mortality, 2 observational studies (64, 66) reported that 8 of 46 patients treated with cinacalcet died, with no deaths considered treatment related. The panel noted the variability in undesirable side effects among patient responses to these medications.

Other Evidence-to-Decision Criteria and Considerations

Although the studies identified used oral and not IV BPs, and were almost exclusively conducted in patients with primary hyperparathyroidism, the panel favors suggesting the use of IV BP because of the superior potency of this drug in patients with parathyroid carcinoma, where the pathophysiology of the hypercalcemia is the same as that in primary hyperparathyroidism. The panel conducted a SR and did not identify any evidence for acceptability, equity, resources, or feasibility. The panel noted that resources will vary based on the severity of HCM and setting. Calcimimetics are easily administered orally in the outpatient setting, whereas zoledronic acid requires resources (IV access; travel; and, in some countries/cities, a nursing or hospital setting). In comparison, Dmab is easily administered subcutaneously in the outpatient setting. Dmab may be anticipated to be more cost-effective than zoledronic

acid (longer effect and fewer doses but potentially more expensive depending on severity of disease and frequency of administration), but there is no evidence in support of this possibility. The interventions are sustainable, and it would be feasible to ensure appropriate use for approved indications. However, there may be important barriers to access to the intervention that may limit the feasibility of implementation and may depend on country-specific health service settings. Refer to "Other Evidence-to-Decision Criteria and Considerations" in Question 1 regarding acceptability and feasibility, adverse effects with IV BPs, and undesirable effects of treatment, including renal failure that might also be relevant to Question 6.

Justification for the Recommendation

The panel agreed that, based on the very low certainty evidence, no important differences were seen in the outcomes with any of the 3 regimens. The panel concluded that the balance of effects, resources required, and equity all varied, but that the treatment would probably be feasible and accessible (see Appendix B).

Question 7. Should addition of a bisphosphonate or denosumab vs no addition of a bisphosphonate or denosumab be used for adults with hypercalcemia due to parathyroid carcinoma in patients not adequately controlled with a calcimimetic?

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 intravenous (IV) bisphosphonate (BP) or denosumab (Dmab) compared with management without an intravenous (IV) bisphosphonate (BP) or denosumab (Dmab). (2⊕OOO)

Summary of Evidence

The evidence summaries, meta-analysis results, and a detailed summary of the evidence and EtD tables can be found online at https://guidelines.gradepro.org/profile/LQ2fsMULJs0.

Benefits and Harms

The SR did not identify any studies that directly address this question. The panel included 1 study that provided indirect evidence due to its study design (18). The retrospective study of Eremkina et al included 10 patients with severe or symptomatic hypercalcemia due to primary hyperparathyroidism, including 2 who had parathyroid carcinoma (68). Five patients received cinacalcet (30 to 120 mg) prior to hospital admission without significant changes in SCa levels. All 10 patients received a single dose of 60 mg Dmab in addition to isotonic saline, and 8 patients continued with cinacalcet at doses of 30 to 60 mg. Normocalcemia was achieved in 4 patients (1 after 3 days, and 3 after 9 days).

Two additional studies used cinacalcet in patients with parathyroid carcinoma previously treated with bisphosphonates (66, 67). In the Silverberg study, treatment-related adverse events were reported in 5 of 29 patients: nausea/vomiting in 2, nausea in 1, hives in 1, and HCM in 1. In the Takeuchi study, all 7 patients reported treatment-related adverse events: nausea in 4, vomiting in 3, and gastroesophageal reflux disease in 2.

Other Evidence-to-Decision Criteria and Considerations

Improved control of HCM with the addition of either an IV BP or Dmab to cinacalcet may result in a decrease in cinacalcet dosing or cinacalcet withdrawal, a superior risk/benefit ratio, and a decrease in hospitalization. Therefore, the cost of therapy may possibly also decrease. In terms of acceptability and feasibility, Dmab is easier to administer (subcutaneous administration) with less need to monitor renal function. However, some institutions and regulatory bodies may limit access to Dmab, which can, in turn, limit its use. The panel noted IV BPs may worsen renal function; in that context, Dmab would be favored in patients with HCM and underlying renal insufficiency (see Table 1). This recommendation is likely acceptable considering that costs or undesirable effects in the short term would be outweighed by potential desirable effects (benefits) in the future. Panel members noted the resources required for such intervention vary by health care setting within a country and between countries, thus leading to variable feasibility worldwide. The impact of this recommendation may also impact health equity negatively (see Appendix B). Refer to "Other Evidence-to-Decision Criteria and Considerations" in Question 1 regarding other considerations of the panel on acceptability and feasibility, adverse effects with IV BPs, and undesirable effects of treatment, including renal failure, that might also be relevant to Question 7.

Justification for the Recommendation

The adverse events often observed during the titration of cinacalcet frequently prevent reaching the effective dosage needed to control HCM. In this context, we expect that the addition of either an IV BP or Dmab therapy will lead to decreased cinacalcet dosing, improvement in control of HCM, and decreased hospitalization and will eventually exert positively impact outcomes of interest, including reduction of adverse events. The panel concluded that the balance of effects, resources required, and equity all varied, but that the treatment would probably be feasible and accessible (see Appendix B).

Question 8. Should a calcimimetic vs no calcimimetic be used for adults with hypercalcemia due to parathyroid carcinoma who are not adequately controlled with a bisphosphonate or denosumab?

Recommendation 8

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

Summary of Evidence

The evidence summaries, meta-analysis results, and a detailed summary of the evidence and EtD tables can be found online at https://guidelines.gradepro.org/profile/N70KA7J8qFM.

Benefits and Harms

The SR did not identify any studies that examined the efficacy of a calcimimetic compared with a placebo in patients with HCM due to parathyroid carcinoma who have already received treatment with a BP or Dmab (18). However, 2 single-arm studies were identified that reported the efficacy of cinacalcet to reduce SCa levels in patients with parathyroid carcinoma.

The study by Silverberg et al reported the efficacy of cinacalcet in 29 patients diagnosed with parathyroid carcinoma, including 23 who had received prior BP treatment for HCM (66). All enrolled patients had prior neck resection. The primary endpoint was the proportion of patients with ≥1 mg/dL (0.25 mmol/L) reduction in SCa. At the end of the study, 18 (62%) patients had achieved the primary outcome, with an average reduction in SCa of 1.7 mg/dL (0.425 mmol/L). Fractures were reported in 6 patients during the study. The most commonly reported medication-related adverse events were nausea, vomiting, dehydration, and headache.

In the study by Takeuchi et al, 5 patients with parathyroid carcinoma were treated with cinacalcet, with 4 completing the study (67). Three patients with parathyroid carcinoma experienced a ≥1 mg/dL (0.25 mmol/L) reduction of SCa. Some patients had received prior BP therapy. The most common adverse events reported were nausea, vomiting, and gastroesophageal reflux.

Other Evidence-to-Decision Criteria and Considerations

In primary hyperparathyroidism due to a single adenoma or multigland hyperplasia, many patients recognize the role of HCM as a contributor to fatigue, depression, and nephrolithiasis. Although the question has not been studied in patients with parathyroid carcinoma, it is likely that patients with HCM due to parathyroid carcinoma also value correction of HCM.

Cinacalcet is available in the United States and most other countries. The panel noted substantial variability in costs by country (17). Most patients with parathyroid carcinoma who are treated with cinacalcet require higher doses, including up to the maximum approved dose of 360 mg daily.

Justification for the Recommendation

The panel noted very low certainty evidence and a lack of high-quality studies on important outcomes. The panel concluded that the balance of effects probably favors the intervention, the cost of resources may be moderate, and equity would vary, but that the treatment would probably be feasible and accessible (see Appendix B).

Research Considerations for Recommendations 6 to 8

Considerations for future research include:

- Head to head RCTs evaluating calcimimetic in addition to a BP or Dmab stratified by severity of HCM, with evaluation to include other patient population details (recurrent/refractory HCM) are needed.
- RCTs should assess clinically important outcomes for this intervention.
- Because of the rarity of this condition, RCTs may require global collaboration.
- Significant gaps in research exist regarding complementary evidence for the treatment of HCM including health services delivery, costs/cost-effectiveness of treatment, patient values and preferences, equity, acceptability, and feasibility.
- Development of calcimimetic administration routes that bypass the gastrointestinal tract leading to better tolerability.

Methods of Development of Evidence-Based Clinical Practice Guidelines

This guideline was developed using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology (77). A detailed description of the Endocrine Society guideline development program can be found online at https://www.endocrine.org/clinical-practice-guidelines/methodology. This methodology includes the use of EtD frameworks to ensure all important criteria are considered when making recommendations (78, 79). The process was facilitated by the GRADEpro Guideline Development Tool (GRADEpro GDT) (80). This Guideline Development Panel (GDP) consisted of 7 content experts representing endocrinology, oncology, and primary care specialties. A patient representative from the United States was to be included on the panel, but, unfortunately, died prior to the first consensus meeting. The patient's spouse and 4 patients completed the surveys that aided the GDP members in prioritizing patient important outcomes (17). Members were identified by the Endocrine Society Board of Directors and the Clinical Guidelines Committee (CGC) and were vetted according to the conflict-of-interest policy for CPGs, which can be found online at https://www.endocrine.org/-/media/endocrine/files/cpg/methodology-page-refresh/conflict_of_interest_cpg_final.pdf (81). This was adhered to throughout the guideline process to manage and mitigate conflicts of interest. Detailed disclosures of panel members and the management strategies implemented during the development process can be found in Appendix C. In addition, the group included a CPG methodologist from the Mayo Evidence-Based Practice Center, who led the team that conducted the SRs and meta-analyses, and a methodologist from the McMaster University MacGRADE Centre, who advised on methodology and moderated the application of the EtD framework and development of the recommendations. All members of the GDP underwent training in guideline participation and GRADE methods led by MacGRADE Centre methodologists and informed by the GRADEpro GDT (82).

GDP members were assigned to lead support to the SR team and present evidence to the GDP for each guideline question. The questions addressed in this guideline were prioritized from an extensive list of potential questions through a survey and discussion; 8 questions were identified as most important. The Mayo Evidence-Based Practice Center conducted a SR for each question and produced GRADE evidence profiles that summarized the body of evidence for each question and the certainty of the evidence (18). The systematic searches for evidence were conducted in September 2020 and updated in April 2022. In parallel to the development of the evidence summaries, the GDP members searched for and summarized research evidence for other EtD criteria, such as patients' values and preferences, feasibility, acceptability, costs/resource use, cost-effectiveness, and health

Table 4. GRADE classification of guideline recommendations

Certainty of evidence	Interpretation
High ⊕⊕⊕⊕	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate ⊕⊕⊕O	We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low ⊕⊕OO	Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
Very Low ⊕OOO	We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

Reprinted with permission from Schünemann HJ, Brożek J, Guyatt GH, Oxman AD. GRADE *Handbook*. Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach. Updated October 2013 (85).

equity. Research evidence summaries noted in the EtD frameworks were compiled using standardized terminology templates for clarity and consistency (83). During a series of video conferences, the GDP judged the balance of benefits and harms, in addition to the other EtD criteria, to determine the direction and strength of the recommendation (Tables 3 and 4 and Appendix B) (83, 84). The panel also agreed on several UGPSs (see Table 2). UGPSs are included when there is information necessary to health care practice, implementation will result in large net positive consequences, collecting and summarizing the evidence would be a poor use of the panel's limited resources, and there is a well-documented clear and explicit rationale (28, 29).

The draft recommendations were posted publicly for external peer review and were reviewed internally by Endocrine Society members, the Society's CGC, representatives of any co-sponsoring organizations, a representative of the Board of Directors, and an Expert Reviewer. Revisions to the guideline were made based on submitted comments and approved by the CGC, the Expert Reviewer, and the representative of the Board of Directors. Finally, the guideline manuscript was reviewed before publication by the *Journal of Clinical Endocrinology and Metabolism*'s publisher's reviewer.

This guideline will be reviewed annually to assess the state of the evidence and determine if there are any developments that would warrant an update to the guideline.

Acknowledgments

The Endocrine Society and the guideline development panel thank Dr. Christopher McCartney and Marie McDonnell, who each served as Clinical Guidelines Committee chair during the development of this clinical practice guideline, for the contributions they made through their leadership and expertise.The Endocrine Society and the guideline development panel also thanks Karen Smith (wife of the late Freddy Smith, United States), Daniele Matellini (Italy), Lina Sioufi (Lebanon), Freddy Smith (United States), and Alberto Zendri (Italy) for completing the patient surveys to prioritize outcomes of relevance to HCM. The panel also thanks Dr. Suzanne Jan De Beur for her expertise in the early stages of the guideline development process. We are also grateful to the American Society of Clinical Oncology (ASCO) for their appointment of an oncologist representative to the panel and for disseminating the guideline for public comment. The panel also thanks Ms Andrea Hickman, manager of Clinical Practice Guidelines for the Endocrine Society, for her guidance and assistance with all aspects of guideline development. We are also grateful for the methodological support provided by the McMaster University MacGRADE Centre in the Endocrine Society's efforts to enhance adherence to GRADE standards, including Holger Schünemann, MD, PhD, Thomas Piggott, MD, MSc, Nancy Santesso, RD, PhD, and Wojtek Wiercioch, MSc, PhD. We also thank M. Hassan Murad, MD for this methodological support for this guideline, and his team at the Mayo Evidence-Based Practice Center, especially Mohamed O. Seisa, MD for their contribution in conducting the evidence reviews for the guideline.

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Disclaimer

The Endocrine Society's clinical practice guidelines are developed to be of assistance to endocrinologists by providing guidance and recommendations for particular areas of practice. The guidelines should not be considered as an all-encompassing approach to patient care and not inclusive of all proper approaches or methods, or exclusive of others. The guidelines cannot guarantee any specific outcome, nor do they establish a standard of care. The guidelines are not intended to dictate the treatment of a particular patient. Treatment decisions must be made based on the independent judgement of health care providers and each patient's individual circumstances. THE ENDOCRINE SOCIETY MAKES EVERY EFFORT TO PRESENT ACCURATE AND RELIABLE INFORMATION. THIS PUBLICATION IS PROVIDED "AS IS" AND THE SOCIETY MAKES NO WARRANTY, EXPRESS OR IMPLIED, REGARDING THE ACCURACY AND RELIABILITY OF THESE GUIDELINES AND SPECIFICALLY EXCLUDES ANY WARRANTIES OF MERCHANTABILITY AND FITNESS FOR A PARTICULAR USE OR PURPOSE, TITLE, OR NON-INFRINGEMENT OF THIRD PARTY RIGHTS. THE SOCIETY, ITS OFFICERS, DIRECTORS, MEMBERS, EMPLOYEES, AND AGENTS SHALL NOT BE LIABLE FOR DIRECT, INDIRECT, SPECIAL, INCIDENTAL, OR CONSEQUENTIAL DAMAGES, INCLUDING THE INTERRUPTION OF BUSINESS, LOSS OF PROFITS, OR OTHER MONETARY DAMAGES, REGARDLESS OF WHETHER SUCH DAMAGES COULD HAVE BEEN FORESEEN OR PREVENTED, RELATED TO THIS PUBLICATION OR THE USE OF OR RELIANCE ON THE INFORMATION CONTAINED HEREIN.

Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during the current study.

Appendix A: Common Terminology Criteria for Adverse Events Grade[1]

Grade based on severity	Corrected serum calcium
Grade 1	Corrected SCa of >ULN to 11.5 mg/dL (2.9 mmol/L); ionized calcium >ULN to 1.5 mmol/L
Grade 2	Corrected SCa of >11.5 to 12.5 mg/dL (2.9 to 3.1 mmol/L); ionized calcium >1.5 to 1.6 mmol/L; symptomatic
Grade 3	Corrected SCa of >12.5 to 13.5 mg/dL (3.1 to 3.4 mmol/L); ionized calcium >1.6 to 1.8 mmol/L; hospitalization indicated
Grade 4	Corrected SCa of >13.5 mg/dL(3.4 mmol/L); ionized calcium >1.8 mmol/L; life-threatening consequences

- Common Terminology Criteria for Adverse Events (CTCAE) grade classifies HCM into 4 grades based on corrected serum calcium (corrected SCa).
- ULN = upper limit of normal (10.8 mg/dL).
- "Corrected calcium" may lead to confusion that the result is due to error and shall be corrected. So, the term "adjusted" calcium is preferred over "corrected" calcium.[2]
- Adjusted total calcium (mg/dL) = total calcium (mg/dL) + 0.8 [4 – albumin(g/dL)] or adjusted total calcium (mmol/L) = total calcium (mmol/L) + 0.02 [40 – albumin (g/L)].[2,3]

[1]CTCAE, US Department of Health and Human Services. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE). Version 5.0. Published: November 27, 2017. (86)
[2]Fraser, William D. (2018). 63. Bone and Mineral Metabolism. In Rifai, Nader. Tietz textbook of clinical chemistry and molecular diagnostics. St. Louis, Missouri: Elsevier. (87)
[3]Maier JD,Levine SN (2015). "Hypercalcemia in the Intensive Care Unit: A Review of Pathophysiology, Diagnosis, and Modern Therapy." *J Intensive Care Med*. 30(5):235-252. (88)

Appendix B: Summary of Evidence to Decision Judgements for all Recommendations

PICO question	Values	Balance of effects	Resources required	Cost-effectiveness	Equity	Accessibility	Feasibility	Recommendation strength and direction
1. Should a bisphosphonate or denosumab vs no treatment with a bisphosphonate or denosumab be used for adults with hypercalcemia of malignancy?	Probably no important uncertainty or variability	Probably favors intervention	Varies	Varies	Varies	Probably yes	Probably yes	Strong recommendation, very low certainty of evidence (1⊕OOO)
2. Should denosumab vs a bisphosphonate be used for adults with hypercalcemia of malignancy?	Probably no important uncertainty or variability	Probably favors intervention	Varies	Varies	Varies	Probably yes	Probably yes	Conditional recommendation, very low certainty evidence (2⊕OOO)
3. Should addition of calcitonin vs no calcitonin be used for adults with severe hypercalcemia of malignancy who will be started on a bisphosphonate or denosumab?	Probably no important uncertainty or variability	Don't know	Moderate costs	No included studies	Varies	Probably yes	Probably Yes	Conditional recommendation, very low certainty evidence (2⊕OOO)
4. Should denosumab vs no denosumab be used for adults with refractory/ recurrent hypercalcemia of malignancy on a bisphosphonate?	Probably no important uncertainty or variability	Don't know	Varies	Varies	Varies	Probably yes	Probably yes	Conditional recommendation, very low certainty evidence (2⊕OOO)
5. Should a bisphosphonate or denosumab vs no bisphosphonate or denosumab be used for adults with hypercalcemia resulting from tumors associated with high calcitriol levels who are already treated with a glucocorticoid?	Probably no important uncertainty or variability	Varies	Varies	Varies	Varies	Probably yes	Probably yes	Conditional recommendation, very low certainty evidence (2⊕OOO)
6. Should a calcimimetic vs a bisphosphonate or denosumab be used for	Probably no important	Varies	Varies	No included studies	Varies	Probably yes	Varies	Conditional recommendation, very low certainty

(*continued*)

Appendix B: Continued

PICO question	Values	Balance of effects	Resources required	Cost-effectiveness	Equity	Accessibility	Feasibility	Recommendation strength and direction
adults with hypercalcemia due to parathyroid carcinoma?	uncertainty or variability							evidence (2⊕OOO)
7. Should addition of a bisphosphonate or denosumab vs no addition of a bisphosphonate or denosumab be used for adults with hypercalcemia due to parathyroid carcinoma in patients not adequately controlled with a calcimimetic?	Probably no important uncertainty or variability	Varies	Varies	No included studies	Varies	Probably yes	Varies	Conditional recommendation, very low certainty evidence (2⊕OOO)
8. Should a calcimimetic vs no calcimimetic be used for adults with hypercalcemia due to parathyroid carcinoma who are not adequately controlled with a bisphosphonate or denosumab?	Probably no important uncertainty or variability	Probably favors intervention	Moderate costs	No included studies	Varies	Probably yes	Yes	Conditional recommendation, very low certainty evidence (2⊕OOO)

Summary

Appendix C: Guideline Development Panel (GDP) Makeup, Roles, Conflicts of Interest (COI), and Management plans

Role	Name	Relevant COI?	Nomination?
Chair	Ghada El-Hajj Fuleihan	No	
Co-Chair	Matthew T. Drake	No	
Member	Gregory A. Clines	No	
Member	Mimi I. Hu	No	
Member	Claudio Marcocci	No	ESE
Member	Hassan Murad	No	Methodologist
Member	Thomas Piggott	No	Methodologist
Member	Catherine Van Poznak	No	ASCO
Member	Joy Wu	No	

Note: The recruited patient representative, Mr. Freddy Smith, unfortunately died prior to the first consensus meeting.

Total number of GDP members = 9
Percent total GDP with relevant COI = 0%

Individual Disclosures, Conflicts, and Management Strategies

Chairs

Chair: Ghada El-Hajj Fuleihan, MD, MPH
American University of Beirut, Beirut, Lebanon
Expertise: Adult endocrinology

Disclosures (2019-2022)

- International Osteoporosis Foundation (IOF): Committee member, Scientific Advisory Committee Panel Member, and Faculty
- American Society for Bone and Mineral Research (ASBMR): Committee member
- International Society for Clinical Densitometry (ISCD): Committee member
- *UpToDate*: Topic author
- *Endocrinology* (journal), Editorial Board
- *Journal of Clinical Endocrinology and Metabolism* (*JCEM*): Editorial Board
- *Metabolism Clinical and Experimental* (journal), Associate Editor
- Abiogen Pharma: Speaker in 2022

Open Payments database: N/A

Assessment and Management

- No relevant conflicts in 12 months prior to selection.

Co-Chair: Matthew T. Drake, MD, PhD
Mayo Clinic, Rochester, MN, USA
Expertise: Adult endocrinology

Disclosures (2019-2022)

- American Board of Internal Medicine (ABIM): Committee work
- US Food & Drug Administration (FDA): Committee work
- Orthopedic Research Society: Advisory Board

- Soft Bones Foundation: Advisory Board
- Rare Bone Disease Alliance: Advisory Board
- *Mayo Clinic Proceedings*: Editor
- *Journal of Bone and Mineral Research* (JBMR): Editor
- *Bone* (journal): Editor
- National Institutes of Health: Grant support
- American Society for Bone and Mineral Research (ASBMR): Chair, Professional Practice Committee

Open Payments Database: https://openpaymentsdata.cms.gov/payment/2021/general/841904571

Assessment and Management

- No relevant conflicts in the 12 months prior to selection.

Guideline Development Panel Members

Gregory A. Clines, MD, PhD
University of Michigan, Ann Arbor, MI, USA
Expertise: Adult endocrinology

Disclosures (2019-2022)

- US Department of Veterans Affairs: Employment
- Endocrine Society: Endocrine Society Self-Assessment Program (EASP) Committee Member
- *JCEM* Case Reports: Editorial Board
- *Clinical Diabetes and Endocrinology*: Associate Editor
- Department of Veterans Affairs: Grant support
- National Institutes of Health: Grant support

Open Payments Database: No entries

Assessment and Management

- No COI relevant to this CPG.
- No management needed.

Mimi I. Hu, MD
University of Texas MD Anderson Cancer Center, Houston, TX, USA
Expertise: Adult endocrinology

Disclosures (2019-2022)

- Loxo Oncology (Loxo Oncology makes/develops small molecule cancer drugs.): Collaborator research; advisory board in 2019
- Blueprint Medicines (Blueprint makes/develops small molecule cancer drugs.): Co-investigator; speaker; advisory board in 2019 to 2020
- Eli Lilly & Company (Eli Lilly makes/markets diabetes treatment drugs.): Primary investigator; advisory board in 2020; consultant in 2020
- University of Arizona Endocrinology Grand Rounds: Speaker in 2020
- Philadelphia Endocrine Society: speaker in 2020
- Veracyte (laboratory testing platform): Consultant in 2020
- Targeted Oncology: Speaker in 2020
- Stony Brook Medical Center Endocrinology Grand Rounds: speaker in 2021
- New England Endocrine Alliance Annual Meeting: Speaker in 2021
- Florida Endocrine Association Annual Meeting: Speaker in 2022
- Thyroid Cancer Survivors' Association (ThyCa): Medical advisor in 2019 to 2022
- International Thyroid Oncology Group (ITOG): MTC Task Force Committee Member in 2019 to 2022; Membership Committee Member in 2022; Protocol Committee Member in 2022
- American Thyroid Association (ATA): Internet Communications, Subcommittee Member in 2019 to 2021; MTC Guidelines Committee Update on Systemic Therapies (Co-chair, 2019-2022)

Open Payments Database: https://openpaymentsdata.cms.gov/physician/1259582

Assessment and Management

- No COI relevant to this CPG.
- No management required.

Claudio Marcocci, MD
Università di Pisa, Pisa, Italy
Expertise: Adult endocrinology
Other: European Society of Endocrinology representative

Disclosures (2019-2022)

- European Society of Endocrinology: Clinical Committee
- *Journal of the Endocrine Society* (JES): Editorial Board
- Shire Italia (Shire makes/markets Natpara (parathyroid hormone), which is not relevant to this CPG): Advisory Board; speaker; primary investigator
- Abiogen Pharma (Abiogen Pharma makes/markets cholecalciferol, alendronate, disodium clodronate, and sodium neridronate): Advisory Board for 1st and 2nd Workshops on Vitamin D (2017 and 2018)
- Ascendis Pharmaceuticals (Ascendis makes/markets TransCon PTH, TransCon hGH, and TransCon C-type natriuretic peptide, along with some cancer treatments) – Primary investigator in 2020
- Takeda: Speaker in 2021
- Asti Incentives & Congress: 5th and 6th Conferences on Controversies in Vitamin D: Advisory Board
- *Journal of Bone and Mineral Research* (JBMR): Editorial Board

Open Payments Database: N/A

Assessment and Management

- No COI relevant to this CPG.
- No management required.

M. Hassan Murad, MD
Mayo Clinic, Rochester, MN, USA
Expertise: Clinical practice guideline methodology

Disclosures (2019-2022)

- Society for Vascular Surgery: Methodology Consultant
- American Society of Hematology: Methodology Consultant
- CHEST: Methodology Consultant
- World Health Organization: Methodology Consultant
- Evidence Foundation: Board Member

Open Payments Database: No entries

Assessment and Management

- No COI relevant to this CPG.
- No management required.

Thomas Piggott, MD
McMaster University, Hamilton, ON, Canada; Queens University, Kingston, ON, Canada; Peterborough Public Health, Peterborough, ON, Canada
Expertise: Clinical practice guideline methodology

Disclosures (2019-2022)

- European Commission Joint Research Centre: Consultant in 2019 to 2020

Open Payments Database: N/A

Assessment and Management

- No COI relevant to this CPG.
- No management required.

Catherine Van Poznak, MD
University of Michigan, Ann Arbor, MI, USA
Expertise: Medical oncology
Other: American Society of Clinical Oncology (ASCO) appointee

Disclosures (2019-2022)

- American Society of Clinical Oncology (ASCO): Committee and guideline panel member (volunteer)
- *UpToDate*: Topic author
- Paget Foundation: Board of Directors
- Bone and Cancer Foundation: Board of Directors
- Bayer Pharmaceuticals (Bayer makes no pharmaceuticals directly related to this CPG): Primary investigator
- American Society of Bone and Mineral Research: Committee
- Multinational Association of Supportive Care in Cancer: Committee

Open Payments Database: https://openpaymentsdata.cms.gov/physician/768369

Assessment and Management

- No COI relevant to this CPG
- No management required

Joy Wu, MD, PhD
Stanford University, Stanford, CA, USA
Expertise: Adult endocrinology

Disclosures (2019-2022)

- Radius Health (Radius health makes/markets abaloparatide [Tymlos]): Research award
- National Institutes of Health: Primary investigator
- Endocrine Society: Board of Directors
- *Journal of Bone and Mineral Research*: Editorial Board
- American Society of Clinical Oncology (ASCO): Guideline panel member
- American Society for Transplantation and Cellular Therapy (ASTCT): Guideline panel member

Open Payments Database: https://openpaymentsdata.cms.gov/physician/380773

Assessment and Management

- No COI relevant to this CPG.
- No management required.

Notes on Prior Panel Members

1. A patient representative with no relevant conflicts of interest was appointed to the panel, but their participation ended in November 2020 due to death.
2. An individual with no relevant conflicts of interest was appointed to the panel, but during the development of the guideline, it came to the attention of the CGC chair that he/she participated on an advisory board for Amgen (Amgen makes/markets denosumab (Prolia, Xgeva) and cinacalcet (Sensipar), which is directly related to this CPG), which posed a relevant conflict of interest that was in violation of the Endocrine Society policy. The individual resigned from the panel in September 2021. All relevant judgements and recommendations made by the panel while this individual was a member were revisited.

PICO Questions vis-à-vis Potential GDP Member Conflicts (June 24, 2020; Updated March 10, 2022)

PICO questions	GDP members with potentially pertinent conflicts related to the PICO
1. Should a bisphosphonate or denosumab vs no treatment with a bisphosphonate or denosumab be used for adults with hypercalcemia of malignancy?	None
2. Should denosumab vs a bisphosphonate be used for adults with hypercalcemia of malignancy?	None
3. Should addition of calcitonin vs no calcitonin be used for adults with severe hypercalcemia of malignancy who will be started on a bisphosphonate or denosumab?	None
4. Should denosumab vs no denosumab be used for adults with refractory/recurrent hypercalcemia of malignancy on a bisphosphonate?	None
5. Should a bisphosphonate or denosumab vs no bisphosphonate or denosumab be used for adults with hypercalcemia resulting from tumors associated with high calcitriol levels who are already treated with a glucocorticoid?	None
6. Should a calcimimetic vs a bisphosphonate or denosumab be used for adults with hypercalcemia due to parathyroid carcinoma?	None
7. Should addition of a bisphosphonate or denosumab vs no addition of a bisphosphonate or denosumab be used for adults with hypercalcemia due to parathyroid carcinoma in patients not adequately controlled with a calcimimetic?	None
8. Should a calcimimetic vs no calcimimetic be used for adults with hypercalcemia due to parathyroid carcinoma who are not adequately controlled with a bisphosphonate or denosumab?	None

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