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Clinical Practice Guideline Systematic Review

Patient and Physician Decisional Factors Regarding Hypercalcemia of Malignancy Treatment: A Novel Mixed-Methods Study

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Abstract

Background: Integrating shared decision making between patients and physicians and incorporating their values and preferences in the development of clinical practice guidelines (CPGs) is of critical importance to optimize CPG implementation and treatment adherence. This applies to many debilitating diseases, including hypercalcemia of malignancy (HCM).

Objective: Evaluate patient and physician values, preferences, and attitudes to better inform CPGs to treat HCM in adults.

Methods: We followed a mixed-methods approach. We conducted a systematic review using 5 databases to identify studies reporting on patient and physician values, costs and resources, feasibility, acceptability, and equity regarding HCM treatment. We also gathered data from different countries on the cost of multiple treatment modalities. We collected data on outcome prioritization from the CPG Working Group. Similarly, we collected data from patients with HCM regarding outcome prioritization and administered a questionnaire to evaluate their attitudes and perceptions toward treatment as well as treatment acceptability and feasibility.

Results: In the systematic review, we included 2 cross-sectional surveys conducted on the same population of physicians who agreed that treating HCM alleviates symptoms and improves quality of life; however, harms and benefits should be thoroughly considered when deciding on the duration of treatment. We also included 2 studies on cost showing that intravenous (IV) bisphosphonate is more cost-effective than a combination of IV bisphosphonate and calcitonin and administration of IV zoledronic acid at home is more cost-effective than other IV bisphosphonates. The cost of zoledronic acid, denosumab, and cinacalcet varied widely among countries and types (brand vs generic). Both the CPG Working Group and patients with HCM agreed that the most important outcomes when deciding on treatment were survival and resolution of HCM, but there was some variability in the ratings for other outcomes.

Conclusion: Using mixed methods, CPG developers can obtain meaningful information regarding evidence to decision criteria. In the case of HCM CPGs, this approach has provided the required contextual information and supported the development of evidence-based recommendations.

Key Words: preferences, cost-effectiveness, feasibility, equity, hypercalcemia, malignancy

Abbreviations: CAD, Canadian dollars; CPG, clinical practice guideline; HCM, hypercalcemia of malignancy; IV, intravenous; RCT, randomized controlled trial; USD, US dollars; WC, writing committee.

Integrating patients' preferences and values into the development of clinical practice guidelines (CPGs) is of critical importance. This improves the quality and ultimately the acceptance and implementation of formulated recommendations as well as adherence to treatment (1-5). Patients and health care providers might have different clinical concerns or priorities; therefore, shared decision making and integrating both points of views is crucial for CPG development (4, 6). This approach is especially beneficial in complex diseases, such as hypercalcemia of malignancy (HCM), which typically require a multidisciplinary team approach to address and compare harms, benefits, and quality of life (2, 7).

CPGs are usually derived from evidence stemming from randomized controlled trials (RCTs), which are considered the highest grading study design (1). However, RCTs do not usually assess patient attitudes and preferences (1, 8). Several attempts to capture these factors have been made, using approaches such as the patient preference trial and

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comprehensive cohort design (8). In such designs, patients are divided into 2 groups: those with strong preferences are given their medication of choice, and those without strong preferences toward a specific treatment are randomized into the different arms (8). This approach is not widely used and therefore evidence and research on patient values and preferences remain scarce. Furthermore, there are currently no established methods to evaluate and grade research and studies on patient preferences (1).

To better inform the Endocrine Society CPGs on HCM treatment in adults, we adopted a mixed-methods approach to evaluate the domains of interest in the GRADE evidence to decision frameworks: patient and physician values, costs and resources, feasibility, acceptability, and equity regarding the different treatment options recommended (6).

Materials and Methods

Systematic Review

The protocol of this systematic review that aims to capture publications on evidence to decision domains relevant to HCM treatment is registered in the PROSPERO registry: CRD42021264371 and published herein (9).

Information sources and search strategies

We conducted a literature search using the following online databases with no language restrictions: Medline (OVID), PubMed, Embase.com, the Cochrane Library, and CINAHL (EBSCO) (9). We used Medical Subject Headings (MeSH) terms and keywords related to malignancy, hypercalcemia, and factors affecting therapy decision, such as patient and physician values, costs and resources, feasibility, acceptability, and equity (Appendix 1A detailed search strategy). As the concept and literature regarding decisional frameworks is relatively new, we limited our search to the preceding 10 years. In addition, we conducted another independent search using Medline (OVID), performed without any time limit, to obtain a more comprehensive scanning of the literature (Appendix 1B) (9). Both search strategies were updated through May 9, 2022.

Eligibility criteria

We included nonrandomized studies, RCTs, reviews, and qualitative studies relevant to HCM treatment in adults. The interventions of interest included bisphosphonates, denosumab, diuretics, calcitonin and calcimimetics, hydration, avoidance of a calcium-rich diet, and vitamin D supplementation. We excluded case reports and studies conducted in the setting of hypercalcemia not related to malignancy.

Variables of interest

Our variables of interest included patient and physician values and preferences (health outcome prioritization), costs and resources, feasibility, acceptability, and equity regarding HCM treatment.

Study selection and evidence abstraction

Three senior authors (M.H.M., T.P., and G.E.H.F.) pilot tested the title and abstract title screening sheet for 100 citations with other authors (A.B., M.R.). Two reviewers (A.B., M.R.) screened the remaining titles and abstracts, and subsequently full texts of included studies, independently and in duplicate using an a priori developed screening sheet. Disagreements between the 2 reviewers were resolved through discussions and seeking help from a third senior author (M.H.M., T.P., or G.E.H.F.).

Two authors (A.B. and M.R.) collected data on the authors, country, study design, study setting, baseline characteristics, sampling methods, administration method, validation, and limitations of each study. We also collected data on each of the prespecified outcomes of interest.

Data synthesis and quality assessment

We assessed the quality of included studies independently and in duplicate (A.B. and G.E.H.F.). For cross-sectional surveys, we used a tool developed by the CLARITY group at McMaster University (10). This tool assesses the following domains: representativeness of sample, adequacy of response rate, missing data, face validity, and construct validity (10). For observational cohort studies, we used the Newcastle–Ottawa quality scale that evaluates 3 main domains: selection, comparability, and outcome/exposure (11).

Cost Acquisition

We collected data on the cost of the following treatments used in HCM: zoledronic acid, pamidronate, denosumab, and cinacalcet. We obtained data from the United States, Europe, Middle East, Australia, South America, and Asia by reaching out to colleagues with expertise in osteoporosis care, from different countries within these regions, for the period between February and October 2021. We developed a template form to capture data on both generic and branded medication costs and collected data on cost per dose. We subsequently calculated the estimated cost per year of therapy. We reported cost using the US dollar (USD) and the country-specific currency to USD exchange rates obtained at the time of data collection. We computed currency exchange rates using Google Finance with data provided by Morningstar Corporate, Refinitiv, and ICE Data Services.

Outcome Prioritization by the Clinical Practice Guideline Writing Committee

The following outcomes of interest for HCM treatment were identified by the CPG writing committee (WC): survival, resolution of hypercalcemia, time to reach normal serum calcium level, quality of life, decrease in skeletal-related events, ability to receive chemotherapy, and adverse events as applicable. Each member of the CPG WC provided a score on a scale from 1 to 9 prioritizing these outcomes: 1 to 3, not important; 4 to 6, important; and 7 to 9, critical.

Patient Questionnaires and Outcome Prioritization

We also asked 5 patients or relatives of patients with hypercalcemia to prioritize the above outcomes identified by the CPG WC. Patients were recruited from the American University of Beirut in Lebanon, the Mayo Clinic in the United States, and the University of Pisa in Italy from the practices of WC members. In addition, we developed and administered a more detailed semistructured questionnaire to 3 of these 5 patients. Because of the lack of validated instruments, we developed a questionnaire based on review of the literature and the expertise of our senior authors (M.H.M., T.P., and G.E.H.F.) (Appendix 2). To explore participant attitudes toward treatments for HCM, we examined different categories. We first

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developed questions about their current treatment, their preferences, and the setting in which they receive their treatments. We also developed questions targeting treatment acceptability and perceptions of feasibility. Finally, we asked participants to rate the importance of the following factors when deciding on a treatment option: correction of hypercalcemia, time to normocalcemia, duration of normocalcemia, effect on mortality and quality of life, side effects, mode of administration, time of administration, setting, physicians' views, and costs and insurance coverage (Appendix 2). Rating was on a scale of 1 to 9: 1 to 3, not important; 4 to 6, important; 7 to 9, critical for decision making.

Results

Systematic Review

We identified a total of 10 268 total publications from our 2 independent searches (Fig. 1). After removing duplicates, we screened a total of 6410 records. We identified 24 potentially eligible full-text articles, from which we included 5 in our systematic review. The list of excluded full texts with corresponding reasons for exclusion is provided in Appendix 3.

Of the included publications, 2 were from a cross-sectional survey conducted in Japan by the same authors (12, 13), 1 was a pilot open-label prospective interventional study from Canada (14), 1 was a retrospective cohort study conducted in the United States (15), and 1 was a review from the United States (16). The outcomes identified in these studies were physician values and beliefs, cost, resources, and feasibility. We did not identify any publication on patient values, acceptability, or equity. The characteristics of the 4 included observational studies are summarized in Table 1 and under "Results."

Physicians' values and beliefs

Mori et al and Shimada et al conducted a cross-sectional survey of 757 physicians recruited from the Japanese Society for Palliative Medicine (12, 13). These physicians are involved in treating HCM and have an average of 21 years of experience. Physician specialties included internal medicine, oncology, surgery, and palliative care. Of the recruited participants, 50.2% responded to the questionnaire (12, 13). The majority (80%) of physicians agreed on treating hypercalcemia in general, and more than 80% believed that treatment improves symptoms, such as nausea, pain, and psychiatric disturbances as well as quality of life (12). However, only 43% (primarily from surgical or oncological specialties) agreed on treating hypercalcemia until a patient's death. They believed that treating hypercalcemia improves lifespan, quality of life, pain, and fatigue (13). Conversely, physicians from specialties such as internal medicine and palliative medicine were less likely to agree with treating hypercalcemia until a patient's death, believing that the efficacy of hypercalcemia treatment decreases with time, and that death from hypercalcemia causes less suffering than the treatment itself (13). Reasons behind the decision for withholding treatment earlier included patient preferences and a previous reaction to treatment (12). The majority (80%) of physicians believed that bisphosphonates are costly, but this did not affect their attitudes or practice (12, 13).

We rated this cross-sectional survey to be of good quality based on the CLARITY tool (Appendix 4A). Although the population recruited was deemed representative, and face validity was confirmed at the start of the study, the response rate was only 50%, and characteristics of respondents were not compared with those of nonrespondents. In addition, the authors noted the presence of missing data in their study and the lack of a validated questionnaire (construct validity, Appendix 4A).

Cost, resources, and feasibility

Marr et al (14) conducted an open-label pilot study to explore the feasibility of zoledronic acid administration to patients with cancer-associated hypercalcemia or bone pain who were referred for palliative care in the community setting rather than at the hospital. They included 12 patients, 10 of whom had HCM. The authors estimated the cost of the administration of 2 other bisphosphonates (pamidronate and clodronate) for comparison. They reported that the cost per dose of zoledronic acid was 620 Canadian dollars (CAD), which was more than twice that of pamidronate (230 CAD) or clodronate (160 CAD). However, administration of zoledronic acid at home requires less nursing time than intravenous (IV) pamidronate and subcutaneous clodronate. The infusion time for zoledronic acid was estimated at 15 minutes, with total nursing time including travel time being 95 minutes compared with 200 minutes for pamidronate and 280 minutes for clodronate. Therefore, total nursing cost was lower when administering zoledronic acid. The authors concluded that, although the total cost for zoledronic acid infusion at home would be higher than that of the other bisphosphonates, zoledronic acid provided at home would be less expensive than receiving any bisphosphonate treatment at the hospital (14). This observational study is of fair quality. It was a pilot study and therefore did not include a representative sample. In addition, it did not include a comparator; therefore, we could not evaluate the comparability domain in the Newcastle–Ottawa risk of bias assessment tool (Appendix 4B).

Khan et al (15) compared bisphosphonate with a combination of IV bisphosphonate and calcitonin for HCM treatment through a retrospective cohort study conducted between 2012 and 2019. The study included 140 participants from a tertiary academic center in the United States: 94 received IV bisphosphonate and 46 received combination therapy. The authors performed a cost analysis and reported that the cost of a 90-mg pamidronate dose was 32 USD vs a 4-mg zoledronic acid dose at 7 USD. The cost for 1 dose of calcitonin (560 U/day) was valued at 3749 USD. The authors estimated that for patients receiving IV bisphosphonate only, cost savings per patient would amount to 11 248 USD compared with receiving combination therapy. The authors concluded that the addition of calcitonin to IV bisphosphonate incurred a significant economic burden but added no clinical benefit. They reported an average cost saving of 291 448 USD per year for not using calcitonin in combination with IV bisphosphonate for the treatment of moderate to severe HCM (15). This observational study is of fair quality and included a representative sample. However, the authors did not provide details, nor did they perform adjusted analyses comparing outcomes in both groups. Furthermore, they did not provide information about the adequacy of follow-up (Appendix 4B).

In a review about HCM treatment published in 1996, Chisholm et al reported the cost of different agents used for hypercalcemia treatment in the United States at that time. Etidronate was the most expensive medication (636 USD), followed by gallium nitrate (514 USD), pamidronate (341 USD), calcitonin (235-360 USD), and plicamycin (157 USD) (16).

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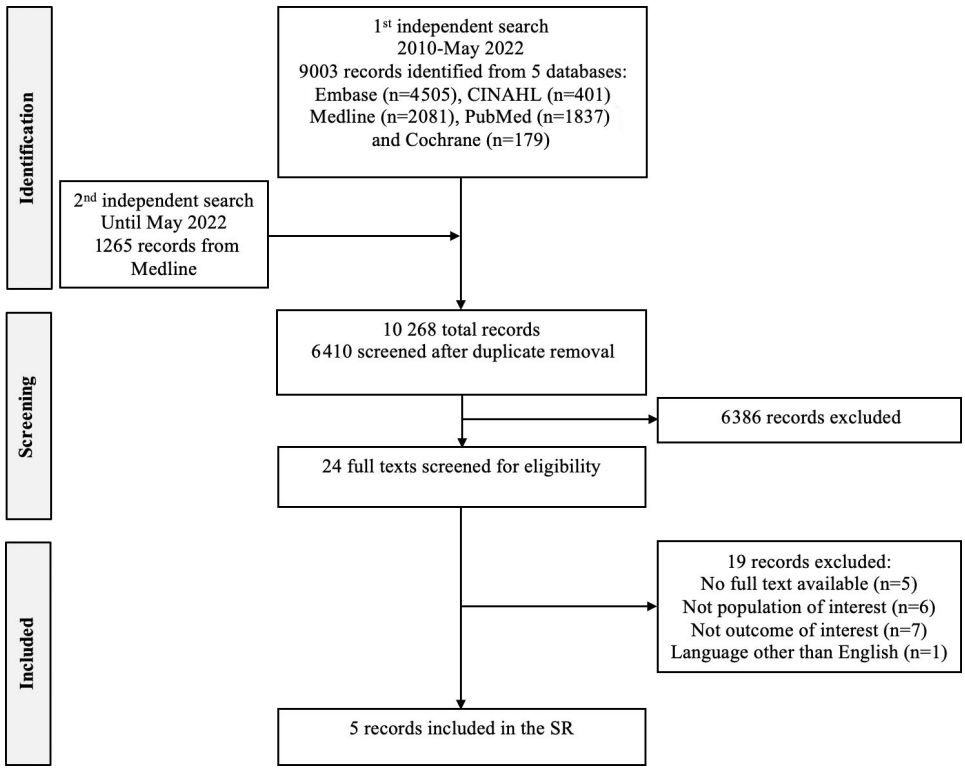

Figure 1. Flow diagram of the literature search and selection process.

Cost of Treatment for Hypercalcemia of Malignancy

We collected cost data from 11 different countries: Lebanon, Kingdom of Saudi Arabia (KSA), Russia, Singapore, India, Italy, France, United Kingdom, United States, Brazil, and Australia. Detailed costs per drug type and country are available in Appendix 5.

The most common zoledronic acid brand used worldwide is Zometa. Data on the cost of Zometa 4 mg was available from 9 countries (Lebanon, KSA, Russia, Italy, France, United Kingdom, United States, Brazil, and Australia). The cost per dose ranged from 64 USD in Australia to 1107 USD in the United States (Fig. 2A). In addition to a lowest cost in Australia, Australian patients pay an even lower price (either 30 USD or 5 USD if they hold a concession card). Zoledronic acid is also available in multiple generic forms (Appendix 5). Cost can be as low as 14 USD/dose in the United Kingdom, 21 USD/dose in India, 28 USD/dose in Lebanon, 33 USD/dose in Russia, 52 USD/dose in Brazil, and 57 USD/dose in the United States (Appendix 5).

The recommended denosumab dose of 120 mg for HCM treatment is only available under the brand name Xgeva. Data on the cost of Xgeva were available from all the countries listed above except KSA. Costs ranged from 182 USD/dose in Brazil to 2823 USD/dose in the United States (Fig. 2B). No generic forms are available for the 120-mg denosumab dose.

The most common cinacalcet brand used worldwide is Mimpara. It is used in Lebanon, Russia, Italy, France, United Kingdom, and Brazil. The cost ranged between 87 USD/30 tablets in Brazil and 326 USD/28 tablets in Italy (Fig. 2C). Cost increases with increasing dose, ranging between 171 USD/30 tablets in Brazil and 603 USD/28 tablets in Italy for 60-mg tablets vs 245 USD/30 tablets in Brazil and 904 USD/28 tablets in Italy for 90-mg tablets (Appendix 5). In the United States, Sensipar is a brand for cinacalcet with a cost of 858 USD/28 tablets for the 30-mg dose (Fig. 2C) and 2576 USD/28 tablets for the 90-mg dose (Appendix 5). Generic cinacalcet is available in Russia, India, Italy, France, United Kingdom, Brazil, and the United States with costs ranging between 19 USD/28 tablets in India and 357 USD/28 tablets in the United States (Appendix 5).

Outcome Prioritization by the Clinical Practice Guideline Writing Committee

The CPG WC consisted of 7 multidisciplinary experts who completed an outcome prioritization table for 8 different clinical scenarios. The rank order was, in general, comparable between scenarios. The CPG WC considered resolution of hypercalcemia, time to obtain normal serum calcium levels, survival, quality of life, and decrease in skeletal-related events to be critical outcomes. Duration of normocalcemia, ability to receive chemotherapy, and adverse events were considered important outcomes. The highest priority score was given to survival, with a median score of 9 and a range of 2 to 9. The lowest priority scores were given to adverse events, with a median of 5 and a range of 2 to 7 (Fig. 3).

Patient Questionnaires and Outcome Prioritization

We recruited 4 patients and 1 patient representative from 3 hospitals. Table 2 represents the characteristics of the 5 included participants. Patient 1 was recruited from the American University of Beirut Medical Center and had been diagnosed with multiple myeloma associated with multiple lytic bone lesions. The patient had developed HCM at presentation, with recurrences along the course of cancer treatment that were treated with zoledronic acid every 4 weeks. Patients 2, 3, and 4 were recruited from the University of Pisa. Patients

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Table 1. Characteristics of included studies from the systematic review[a]

Author, year (country)	Study design	Sampling method	Sample size (n)	Age, mean ± SD, or median (range)	Cause of hypercalcemia (cancer)	Type of treatment	Outcomes assessed	Quality assessment[b]
Shimada, 2015 (Japan) (13) Mori, 2016 (Japan) (12)	Cross-sectional survey	Physicians from the Japanese Society for Palliative Medicine involved in treating hypercalcemia were requested to complete and return the questionnaire	757	Mean clinical expertise 21 ± 8.3 years	N/A	N/A	Physician values and preferences	Good
Marr, 2010 (Canada) (14)	Pilot open-label interventional study	Patients with symptomatic tumor-induced hypercalcemia (n = 10) or severe malignant bone pain (n = 2) referred to the community-based palliative care consult team were screened for eligibility to participate	12	66 (46-81)	Genitourinary (n = 3), head and neck (n = 3), lung (n = 2), breast (n = 2), melanoma (n = 1), and unknown (n = 1)	Zoledronic acid	Cost and resources Feasibility	Fair
Khan, 2021 (United States) (15)	Retrospective observational cohort	Data were collected as part of routine care of HCM and screened for inclusion between August 1, 2012 and July 31, 2019.	140 (G1, 94; G2, 46)	G1: 62 (54-72) G2: 58 (46-73)	G1: solid tumor (84%), hematologic (14%), unclear (1%), both (1%) G2: solid tumor (67%), hematologic (29%), unclear (4%), both (0%)	G1: IV bisphosphonate G2: IV bisphosphonate + calcitonin	Cost and resources	Fair

Abbreviations: HCM, hypercalcemia of malignancy; G1, group 1; G2, group 2; IV, intravenous; N/A: not available.
[a]The study by Chisholm et al (16) is a review and is detailed in the text.
[b]See Appendix 4 for further details on risk of bias and quality assessment of included studies.

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2 and 3 had parathyroid carcinoma. They were diagnosed with recurrent hypercalcemia requiring 2 parathyroidectomies, revealing the parathyroid carcinoma. For the recurrent hypercalcemia, patient 2 was treated with denosumab every 4 weeks, while patient 3 was treated with a combination of cinacalcet and bisphosphonate for 6 months. Patient 4 had HCM from metastatic breast cancer. Patient 5 had been treated for metastatic parathyroid carcinoma at the Mayo Clinic for 9.5 years and had required numerous treatments including antiresorptive medications, repeated debulking surgeries, and ethanol ablation procedures for disease management. The patient died prior to completion of data collection, and we therefore gathered subsequent information from the patient's spouse.

The 5 patients prioritized the outcomes identified by the CPG WC. They gave survival (median = 9; range 8-9) and quality of life (median = 9; range 7-9) the highest priority scores. These were followed by resolution of hypercalcemia (median = 8; range 7-9), time to normal serum calcium levels (median = 7; range 7-9), and duration of normal calcium levels (median = 6.5; range 5-8). There was some variability in the ratings of the remaining 3 outcomes: decrease in skeletal related outcomes, side effects, and ability to receive chemotherapy. Two patients (patients 2 and 3) rated these outcomes as not important with a score of 1, while the other 3 rated these as critical outcomes with a score of 8 to 9 (Table 3).

Patients 1, 2, and 3 also responded to our semistructured questionnaire. Patients 1 and 2 preferred a denosumab regimen, which they described as more convenient than the other available regimens. Patient 3 did not have any preference regarding treatment regimen. Patient 1 preferred receiving treatment in a hospital under the supervision of a health care professional, considering this setting safer. Patient 2 preferred self-administering denosumab at home. Patient 3 preferred a combination of settings: self-administration at home but hospital treatment if experiencing severe symptoms.

Patient 1, who was treated with zoledronic acid, reported acceptable side effects in the form of an acute phase reaction, which gradually decreased with subsequent infusions. Patient 1 would have preferred an oral or injectable treatment over an IV regimen and a greater interval (such as every 6 weeks) between infusions. However, the patient added that they "would do anything to optimize treatment." They did not consider duration of treatment, cost, or travel time as barriers to receiving treatment because of living in close proximity to the hospital and being fully covered by insurance. Patients 2 and 3 reported that their treatment regimens were acceptable in terms of benefits, side effects, cost, and implementation. However, patient 3 recognized both the injection scheduled intervals and cinacalcet side effects as potential barriers.

The interviewed patients considered the effects on mortality and quality of life, insurance coverage, physician opinions, correction of hypercalcemia, and duration of normal serum calcium levels as critical factors with respect to choosing a specific treatment (Table 4).

Discussion

We adopted a novel mixed-methods approach to gather information on various domains included in the evidence to decision framework as they pertain to stakeholders involved in HCM treatment. In our approach, we combined a systematic review of studies assessing physician preferences and attitudes with questionnaires and surveys addressed to patients and physicians to close knowledge gaps on specific domains. Our study reveals internal consistency with comparable outcome prioritization by physicians and patients regarding HCM treatment for the outcomes of survival and the resolution of HCM, albeit with some variability for other outcomes. In general, both physicians and patients deemed HCM treatments feasible and acceptable. Physicians agreed on treating HCM to improve quality of life; however, they stressed the importance of weighing risks and benefits when it comes to duration. We identified only 2 studies that reported on feasibility and cost and complemented findings with primary data collection for commonly used drugs for HCM treatment. Cost varied between brand name and generic medications and across countries from 5 continents. The difference in cost could be as much as 5- to 10-fold higher, with a trend for the costliest medications being in the United States.

Although physician and patient attitudes and beliefs were not always aligned for the treatment of chronic diseases, current medical practice has evolved steadily toward a more patient-centered approach (17, 18). Patient-centered care encourages shared decision making and considering the patient's wishes, preferences, and desires when deciding on a specific treatment (19) to potentially optimize both compliance and health outcomes (20). This approach has become a hallmark in patients with devastating diseases, particularly malignancy (21). In the identified cross-sectional studies, most physicians agreed on treating patients with HCM to alleviate symptoms and improve quality of life. However, as treatment effects do gradually decrease, some physicians agreed to withhold treatment in accordance with patient preferences because, at that point, negative side effects outweigh benefits (12, 13). Similarly, all subjects rated survival and quality of life as the most important outcomes of HCM treatment. However, we noticed some variability in the scoring of the following outcomes: decrease in skeletal-related outcomes, side effects, and ability to receive chemotherapy. These differences might be explained by patients' individual disease status. Indeed, 2 patients had parathyroid carcinoma, a slowly progressing disease for which there is no effective chemotherapy, but bone metastases are uncommon and therefore no significant adverse events related to medical therapy (unless high doses of cinacalcet are used) would be expected. These patients therefore rated these outcomes as not important. Conversely, the other 3 patients with multiple myeloma, metastatic breast cancer, and metastatic parathyroid carcinoma rated these outcomes as critical.

There have been variable reports regarding the balance of harms and benefits when considering treatments in other disease paradigms. Women with osteoporosis rated the importance of effectiveness and side effects equally (5), whereas patients on antithrombotic medications placed higher value on treatment than on side effects (22). Three patients participated in our questionnaire that assessed values and preferences in a more global approach including acceptability, feasibility, cost, and insurance coverage. Two agreed that denosumab is the preferred and most convenient treatment regimen. This is in line with findings from a systematic review on female patients' preferences regarding osteoporosis treatment. Barrionuevo et al reported that patients preferred less frequent and more convenient treatment options regardless of route of administration (5).

We included 2 studies reporting on the cost of HCM treatment in our systematic review. IV bisphosphonate was found

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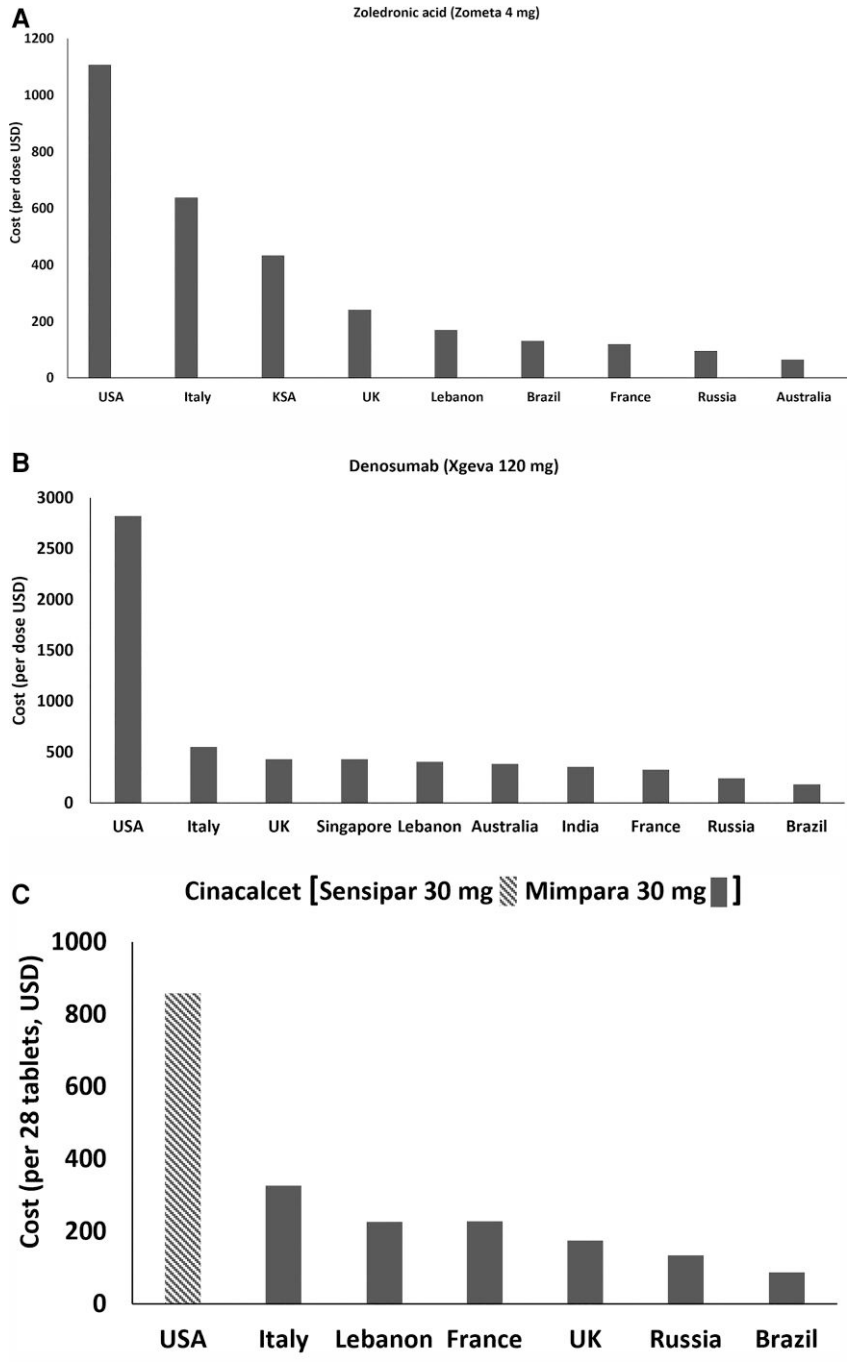

Figure 2. Cost of brand medications for treatment of hypercalcemia of malignancy in USD per country. (A) Zoledronic acid, (B) Denosumab (C) Cinacalcet.

to be more cost-effective than the combination of IV bisphosphonate and calcitonin (15). In addition, administration of IV zoledronic acid at home was found to be more cost-effective than other IV bisphosphonates (14). We also collected cost data for different medications approved for HCM treatment across different countries and continents. IV zoledronic acid and intramuscular denosumab were generally more expensive than oral cinacalcet. Cost varied considerably by country and by type (brand vs generic). Furthermore, we interviewed 3 patients who thought that cost and insurance coverage are important aspects in deciding treatment options. Increasing medication costs is a leading cause of nonadherence, which leads to increased disease burden and increased mortality (23). Therefore, several strategies should be implemented to avoid cost-related nonadherence. These include prescription assistance programs in addition to educating prescribing physicians on the cost of medications and the importance of both having open discussions with patients regarding their ability to afford these medications and of providing alternatives (24).

There are several limitations to our study. They mostly arise from intrinsic limitations of the few identified studies. These include small sample size, nonrepresentative samples, and lack of statistical comparisons between groups in the cohort studies or lack of validated tools in the cross-sectional surveys. We rated the quality of the studies identified as fair to good

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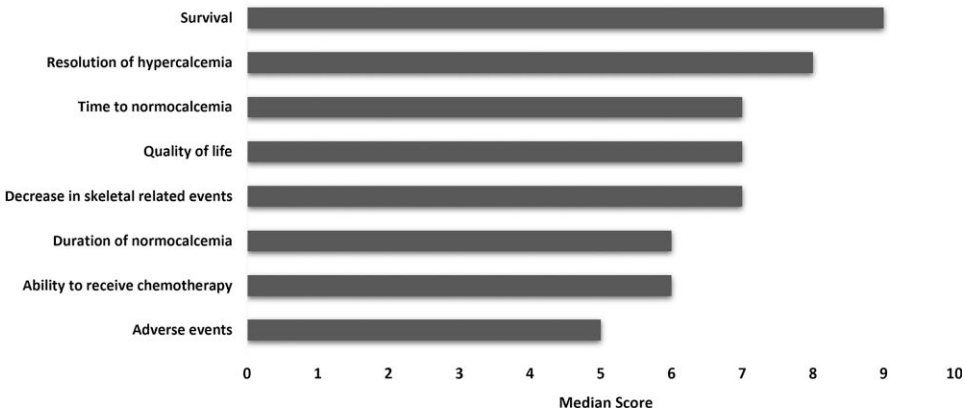

Figure 3. Outcome prioritization by the clinical practice guideline writing group. Prioritization scores: 1 to 3 not important; 4 to 6 important; and 7 to 9 critical.

Table 2. Characteristics of included patients

	Patient 1	Patient 2	Patient 3	Patient 4[a]	Patient 5
Site (country)	American University of Beirut Medical Center (Lebanon)	University of Pisa (Italy)	University of Pisa (Italy)	University of Pisa (Italy)	Mayo Clinic (United States)
Main diagnosis	Multiple myeloma	Parathyroid carcinoma	Parathyroid carcinoma	Metastatic breast cancer	Metastatic parathyroid carcinoma
Malignancy treatment	Bone marrow transplants (2), chemotherapy, and immunotherapy	Parathyroidectomy	Parathyroidectomy	N/A	Repeated debulking surgeries and ethanol ablation
Hypercalcemia course	Recurrent	Recurrent	Recurrent	N/A	N/A
Hypercalcemia treatment	Zoledronic acid every 4 weeks	Denosumab every 4 weeks	Combination of cinacalcet and bisphosphonate	N/A	Antiresorptive medications

N/A: not available.
[a]Detailed information on patient 4 was not available.

Table 3. Outcome prioritization by patients[a] with hypercalcemia of malignancy

	Patient 1 (multiple myeloma)	Patient 2 (parathyroid carcinoma)	Patient 3 (parathyroid carcinoma)	Patient 4 (metastatic breast cancer)	Patient 5 (metastatic parathyroid carcinoma)	Mean	Median
Survival	9	9	8	9	8	8.6	9
Quality of life	9	8	7	9	9	8.4	9
Resolution of hypercalcemia	9	9	8	8	7	8.2	8
Time to normocalcemia	7	7	7	8	9	7.6	7
Duration of normocalcemia	8	5	N/A	8	5	6.5	6.5
Decrease in skeletal related events	9	1	1	9	9	5.8	9
Adverse events	9	1	1	9	8	5.6	8
Ability to receive chemotherapy	8	1	1	8	9	5.4	8

[a]Patient characteristics are detailed in Table 2 and under "Results."

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Table 4. Prioritization of factors by patients with hypercalcemia of malignancy affecting decision making in their treatment

	Patient 1	Patient 2	Patient 3	Mean	Median
Correction of hypercalcemia	7	6	9	7.3	7
Time to normal calcium levels	6	5	5	5.3	5
Duration of normal calcium levels	9	5	7	7	7
Effect on mortality	9	8	9	8.7	9
Effect on quality of life	8	8	9	8.3	8
Side effects	8	4	6	6	6
Mode of administration	7	6	3	5.3	6
Time of treatment administration	6	4	3	4.3	4
Setting of treatment administration (home vs hospital)	9	4	3	5.3	4
Physician opinion	9	7	8	8	8
Cost	7	7	3	5.7	7
Insurance coverage	8	8	9	8.3	8

but were unable to assess construct validity of the instruments used. Furthermore, we identified only a small number of studies related to our topic of interest with different outcomes. We were also unable to identify rigorously conducted and representative studies investigating the cost-effectiveness of the treatment drugs and publications evaluating acceptability and feasibility for their use. We therefore resorted to narrative report. In addition, only a small number of patients participated in our survey and questionnaire, so our results might not be generalizable to the whole population with HCM. However, to increase representativeness, we included patients with different HCM etiologies, on different treatment modalities, and from different countries.

Our study has important strengths. It is based on a comprehensive systematic review, which allowed us to map and synthesize available data on this topic. It used a novel mixed-methods approach that facilitated the combination of both qualitative and quantitative data simultaneously. This approach enabled us to better understand, clarify, and corroborate findings across different methods and close the care gap.

Data regarding physician and patient values and preferences is scarce in general. Patients are vital constituents in decision making, and more studies are needed to investigate their attitudes, beliefs, preferences, and values regarding treatment options of life-threatening or extensive diseases such as HCM. Physician and patient assessments were aligned for the outcomes of survival, quality of life, and resolution of hypercalcemia, but they varied for other health outcomes. Physician specialty and patient disease health status and health care setting impact the decisional framework with regards to HCM treatment. Our study helps inform the development of CPGs for the management of HCM and may guide prescribing physicians in their practices.

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Disclosure

The authors declare no conflict of interest.

Data Availability

Some or all data generated or analyzed during this study are included in this published article.

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Appendix 1A. Original search strategies

1—Pubmed

#12 Search #10 AND #11

#11 Search 2010/04:2020/04 [crdt]

#10 Search #8 AND #9

#9 Search "Attitude to Health" [MESH] OR Patient Participation [MESH:NOEXP] OR Patient Preference [MESH:NOEXP] OR Cost-Benefit Analysis [MESH:NOEXP] OR preference* [tw] OR choice* [tw] OR valu* [tw] OR expectation* [tw] OR attitude* [tw] OR acceptab* [tw] OR knowledg* [tw] OR sustain* [tw] OR barrier* [tw]] OR access* [tw] OR implement* [tw] OR inequit* [tw] OR disparit* [tw] OR inequalit* [tw] OR income [tw] OR socioeconomic* [tw] OR gamble [tw] OR utility* [tw]OR health sat* [tw] OR adhere* [tw] OR quality life [tw] OR Qol [tw] OR willing* [tw]OR burden* [tw] OR satisf* [tw] OR opinion* [tw] OR Patient participation* [tw] OR patients participation* [tw] OR user participation* [tw] OR users participation* [tw] OR health participation* [tw] OR healthcare participation* [tw] OR health-care participation* [tw] OR Patient perception* [tw] OR patients perception* [tw] OR user perception* [tw] OR users perception* [tw] OR health perception* [tw] OR healthcare perception* [tw] OR health-care perception* [tw] OR (decision* [tw] AND (board* [tw] OR tool* [tw] OR analy* [tw] OR support [tw]) OR equit* [tw] OR equality [tw] OR feasib* [tw] OR perspective* [tw] OR cost* [tw] OR resource* [tw]) OR balance sect* [tw] OR discrete choice* [tw] OR ((("decision making" [mesh] OR decision mak* [tw]) AND (patient* [tw] OR user* [tw] OR Famil* [tw] OR customer* [tw] OR consumer* [tw] OR client* [tw] OR men [tw] OR man [tw] OR women [tw] OR woman [w] OR individual [tw] OR individuals [tw]))

#8 Search #6 OR #7

#7 Search HHM [tw] or LOH [tw]

#6 Search #1 AND #5

#5 Search #2 OR #3 OR #4

#4 Search (calcinos* [tw] OR hypercalcemi* [tw])

#3 Search Hypercalcemia [MESH:NOEXP]

#2 Search Calcinosis [MESH:NOEXP]

#1 Search (cancer* [tw] OR carcinoma* [tw] OR adenocarcinoma* [tw] OR hepatocarcinoma* [tw] OR carcinosarcoma* [tw] OR sarcoma* [tw] OR histiocytoma* [tw] OR fibrosarcoma* [tw] OR osteosarcoma* [tw] OR chondrosarcoma* [tw] OR lymphosarcoma* [tw] OR rhabdomyosarcoma* [tw] OR leukemi* [tw] OR leukaemi* [tw] OR erythroleukem* [tw] OR erythroleukaem* [tw] OR lymphoma* [tw] OR melanoma* [tw] OR hodgkin* [tw] OR multiple myeloma* [tw] OR mesothelioma* [tw] OR neoplas* [tw] OR malignan* [tw] OR metastas* [tw] OR carcinoid* [tw] OR neuroblastoma* [tw] OR Mycosis Fungoid* [tw] OR Sezary Syndrome* [tw] OR Retinoblastoma* [tw] OR pheochromocytoma* [tw] OR nephroblastoma* [tw] OR chORiocarcinoma* [tw] OR Pleuropulmonary Blastoma* [tw] OR glioblastoma* [tw] OR glioma* [tw] OR astrocytoma* [tw] OR ependymoma* [tw] OR medulloblastoma* [tw] OR meningioma* [tw] OR craniopharyngioma* [tw] OR myelodysplastic [tw] OR myeloproliferative [tw] OR macroglobulinemi* [tw] OR macroglobulinaemi* [tw] OR pineoblastoma* [tw] OR oncol* [tw] OR cyst [tw] OR tumor* [tw] OR tumour* [tw] OR Neoplasm [MESH]

2—Medline (OVID)

1 (cancer* or carcinoma* or adenocarcinoma* or hepatocarcinoma* or carcinosarcoma* or sarcoma* or histiocytoma* or fibrosarcoma* or osteosarcoma* or chondrosarcoma* or lymphosarcoma* or rhabdomyosarcoma* or leuk?emi* or erythroleukem* or erythroleukaem* or lymphoma* or melanoma* or hodgkin* or "multiple myeloma" or mesothelioma* or neoplas* or malignan* or metastas* or carcinoid* or neuroblastoma* or (Mycosis adj Fungoid?s) or (Sezary adj Syndrome) or Retinoblastoma* or pheochromocytoma* or nephroblastoma* or choriocarcinoma* or (Pleuropulmonary adj Blastoma?) or glioblastoma* or glioma* or astrocytoma* or ependymoma* or medulloblastoma* or meningioma* or craniopharyngioma* or myelodysplastic or myeloproliferative or macroglobulinemi* or macroglobulinaemi* or pineoblastoma* or oncol* or cyst or tumo?r*).mp. or exp Neoplasm/

2 Calcinosis/ or hypercalcemia/ or (calcinos?s or hypercalcemi*).mp.

3 (HHM or LOH).mp.

4 1 and 2

5 3 or 4

6 exp Attitude to Health/ or Patient Participation/ or Patient Preference/ or Cost-Benefit Analysis/ or (preference* or choice* or valu* or expectation? or attitude* or acceptab* or knowledg* or sustain* or barrier* or access* or implement* or inequit* or disparit* or inequalit* or income or socioeconomic* or gamble or utilit* or (health adj stat*) or adhere* or (quality adj2 life) or Qol or willing* or burden* or satisf* or opinion* or ((patient* or user* or health*) adj3 (participat* or perce*)) or (Decision adj3 (board* or tool* or analy* or support)) or equit* or equality or feasib* or perspective* or cost* or resource* or (balance adj1 sect*) or (discrete* adj1 choice*)).mp. or ((exp Decision Making/ or (decision* adj1 mak*).mp.) and (patient* or user* or Famil* or customer* or consumer* or client* or women or men or individual?).mp.)

7 5 and 6

8 limit 7 to ez="20100407-20200407"

3—Embase.com

#14. #12 AND #13

#13. [1-4-2010]/sd

#12. #10 AND #11

#11. 'attitude to health'/exp OR 'patient participation'/de OR 'patient preference'/de OR 'cost benefit analysis'/de OR preference*:ti,ab,kw OR choice*:ti,ab,kw OR valu*:ti,ab,kw OR expectation$:ti,ab,kw OR attitude*:ti,ab,kw OR acceptab*:ti,ab,kw OR knowledg*:ti,ab,kw OR sustain*:ti,ab,kw OR barrier*:ti,ab,kw OR access*:ti,ab,kw OR implement*:ti,ab,kw OR inequit*:ti,ab,kw OR disparit*:ti,ab,kw OR inequalit*:ti,ab,kw OR income:ti,ab,kw OR socioeconomic*:ti,ab,kw OR gamble:ti,ab,kw OR utilit*:ti,ab,kw OR ((health NEXT/0 stat*):ti,ab,kw) OR adhere*:ti,ab,kw OR ((quality NEAR/2 life):ti,ab,kw) OR qol:ti,ab,kw OR willing*:ti,ab,kw OR burden*:ti,ab,kw OR satisf*:ti,ab,kw OR opinion*:ti,ab,kw OR (((patient* OR user* OR health*) NEAR/3 (participat* OR perce*)):ti,ab,kw) OR ((decision NEAR/3 (board* OR tool* OR analy* OR support)):ti,ab,kw) OR equit*:ti,ab,kw OR equality:ti,ab,kw OR feasib*:ti,ab,kw OR perspective*:ti,ab,kw OR cost:ti,ab,kw OR resource*:ti,ab,kw OR ((balance NEAR/1 sect*):ti,ab,kw) OR ((discrete* NEAR/1 choice*):ti,ab,kw) OR ('decision making'/exp

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AND (patient*:ti,ab,kw OR user*:ti,ab,kw OR famil*:ti,ab,kw OR customer*:ti,ab,kw OR consumer*:ti,ab,kw OR client*:ti,ab,kw OR women:ti,ab,kw OR men OR individual*:ti,ab,kw)) OR (((decision* NEAR/1 mak*):ti,ab,kw) AND (patient*:ti,ab,kw OR user*:ti,ab,kw OR famil*:ti,ab,kw OR customer*:ti,ab,kw OR consumer*:ti,ab,kw OR client*:ti,ab,kw OR women:ti,ab,kw OR men:ti,ab,kw OR individual*:ti,ab,kw))

#10. #8 OR #9

#9. #3 AND #7

#8. hhm:ti,ab,kw OR loh:ti,ab,kw

#7. #4 OR #5 OR #6

#6. calcinos$s:ti,ab,kw OR hypercalcemi:ti,ab,kw

#5. 'hypercalcemia'/de

#4. 'calcinosis'/de

#3. #1 OR #2

#2. 'neoplasm'/exp

#1. cancer*:ti,ab,kw OR carcinoma*:ti,ab,kw OR adenocarcinoma*:ti,ab,kw OR hepatocarcinoma*:ti,ab,kw OR carcinosarcoma*:ti,ab,kw OR sarcoma*:ti,ab,kw OR histiocytoma*:ti,ab,kw OR fibrosarcoma*:ti,ab,kw OR osteosarcoma*:ti,ab,kw OR chondrosarcoma*:ti,ab,kw OR lymphosarcoma*:ti,ab,kw OR rhabdomyosarcoma*:ti,ab,kw OR leukemi*:ti,ab,kw OR leukaemi*:ti,ab,kw OR erythroleukem*:ti,ab,kw OR erythroleukaem*:ti,ab,kw OR lymphoma*:ti,ab,kw OR melanoma*:ti,ab,kw OR hodgkin*:ti,ab,kw OR 'multiple myeloma':ti,ab,kw OR mesothelioma*:ti,ab,kw OR neoplas*:ti,ab,kw OR malignan*:ti,ab,kw OR metastas*:ti,ab,kw OR carcinoid*:ti,ab,kw OR neuroblastoma*:ti,ab,kw OR ((mycosis NEXT/0 fungoid$s):ti,ab,kw) OR ((sezary NEXT/0 syndrome):ti,ab,kw) OR retinoblastoma*:ti,ab,kw OR pheochromocytoma*:ti,ab,kw OR nephroblastoma*:ti,ab,kw OR choriocarcinoma*:ti,ab,kw OR ((pleuropulmonary NEXT/0 blastoma$):ti,ab,kw) OR glioblastoma*:ti,ab,kw OR glioma*:ti,ab,kw OR astrocytoma*:ti,ab,kw OR ependymoma*:ti,ab,kw OR medulloblastoma*:ti,ab,kw OR meningioma*:ti,ab,kw OR craniopharyngioma*:ti,ab,kw OR myelodysplastic:ti,ab,kw OR myeloproliferative:ti,ab,kw OR macroglobulinemi*:ti,ab,kw OR macroglobulinaemi*:ti,ab,kw OR pineoblastoma*:ti,ab,kw OR oncol*:ti,ab,kw OR cyst:ti,ab,kw OR tumo$r*:ti,ab,kw

4—CINAHL (EBSCO)

S29 MW S14 AND S28

S28 S15 OR S16 OR S17 OR S18 OR S24 OR S25 OR S26 OR S27

S27 MW (preference* OR choice* OR valu* OR expectation# OR attitude* OR acceptab* OR knowledg*) OR sustain* OR barrier* OR access* OR implement* OR inequit* OR disparit* OR inequalit* OR income OR socioeconomic* OR gamble OR utilit* OR ((health W0 stat*)) OR adhere* OR ((quality N2 life)) OR qol OR willing* OR burden* OR satisf* OR opinion* OR (((patient* OR user* OR health*) N3 (participat* OR perce*))) OR ((decision N3 (board* OR tool* OR analy* OR support))) OR equit* OR equality OR feasib* OR perspective* OR cost OR resource* OR ((balance N1 sect*)) OR ((discrete* N1 choice*)) OR (((decision* N1 mak*)) AND (patient* OR user* OR famil* OR customer* OR consumer* OR client* OR women OR woman OR men OR man OR individual*))

S26 AB (preference* OR choice* OR valu* OR expectation# OR attitude* OR acceptab* OR knowledg*) OR sustain* OR barrier* OR access* OR implement* OR inequit* OR disparit* OR inequalit* OR income OR socioeconomic* OR gamble OR utilit* OR ((health W0 stat*)) OR adhere* OR ((quality N2 life)) OR qol OR willing* OR burden* OR satisf* OR opinion* OR (((patient* OR user* OR health*) N3 (participat* OR perce*))) OR ((decision N3 (board* OR tool* OR analy* OR support))) OR equit* OR equality OR feasib* OR perspective* OR cost OR resource* OR ((balance N1 sect*)) OR ((discrete* N1 choice*)) OR (((decision* N1 mak*)) AND (patient* OR user* OR famil* OR customer* OR consumer* OR client* OR women OR woman OR men OR man OR individual*))

S25 TI (preference* OR choice* OR valu* OR expectation# OR attitude* OR acceptab* OR knowledg*) OR sustain* OR barrier* OR access* OR implement* OR inequit* OR disparit* OR inequalit* OR income OR socioeconomic* OR gamble OR utilit* OR ((health W0 stat*)) OR adhere* OR ((quality N2 life)) OR qol OR willing* OR burden* OR satisf* OR opinion* OR (((patient* OR user* OR health*) N3 (participat* OR perce*))) OR ((decision N3 (board* OR tool* OR analy* OR support))) OR equit* OR equality OR feasib* OR perspective* OR cost OR resource* OR ((balance N1 sect*)) OR ((discrete* N1 choice*)) OR (((decision* N1 mak*)) AND (patient* OR user* OR famil* OR customer* OR consumer* OR client* OR women OR woman OR men OR man OR individual*))

S24 S19 AND S23

S23 S20 OR S21 OR S22

S22 MW patient* OR user* OR famil* OR customer* OR consumer* OR client* OR women OR woman OR men OR man OR individual*

S21 AB patient* OR user* OR famil* OR customer* OR consumer* OR client* OR women OR woman OR men OR man OR individual*

S20 TI patient* OR user* OR famil* OR customer* OR consumer* OR client* OR women OR woman OR men OR man OR individual*

S19 (MH "Decision Making+")

S18 (MH "Cost Benefit Analysis")

S17 (MH "Patient Preference")

S16 (MH "Consumer Participation")

S15 (MH "Attitude to Health+")

S14 S12 OR S13

S13 TI HHM OR LOH

S12 S10 AND S11

S11 S5 OR S6 OR S7 OR S8 OR S9

S10 S1 OR S2 OR S3 OR S4

S9 MW calcinos* OR hypercalcemi*

S8 AB calcinos* OR hypercalcemi*

S7 TI calcinos* OR hypercalcemi*

S6 (MH "Hypercalcemia")

S5 (MH "Calcinosis")

S4 MW TI (cancer* OR carcinoma* OR adenocarcinoma* OR hepatocarcinoma* OR carcinosarcoma* OR sarcoma* OR histiocytoma* OR fibrosarcoma* OR osteosarcoma* OR chondrosarcoma* OR lymphosarcoma* OR rhabdomyosarcoma* OR leukemi* OR leukaemi* OR erythroleukem* OR erythroleukaem* OR lymphoma* OR melanoma* OR hodgkin* OR 'multiple myeloma' OR mesothelioma* OR neoplas* OR malignan* OR metastas* OR carcinoid* OR neuroblastoma* OR ((mycosis W0 fungoid#s)) OR ((sezary W0 syndrome)) OR retinoblastoma* OR pheochromocytoma* OR nephroblastoma* OR choriocarcinoma* OR ((pleuropulmonary W0 blastoma#)) OR glioblastoma* OR glioma* OR astrocytoma* OR ependymoma* OR medulloblastoma* OR meningioma* OR craniopharyngioma* OR myelodysplastic OR myeloproliferative OR macroglobulinemi* OR macroglobulinaemi* OR pineoblastoma* OR oncol* OR cyst OR tumo#r*)

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S3 AB TI (cancer* OR carcinoma* OR adenocarcinoma* OR hepatocarcinoma* OR carcinosarcoma* OR sarcoma* OR histiocytoma* OR fibrosarcoma* OR osteosarcoma* OR chondrosarcoma* OR lymphosarcoma* OR rhabdomyosarcoma* OR leukemi* OR leukaemi* OR erythroleukem* OR erythroleukaem* OR lymphoma* OR melanoma* OR hodgkin* OR 'multiple myeloma' OR mesothelioma* OR neoplas* OR malignan* OR metastas* OR carcinoid* OR neuroblastoma* OR ((mycosis W0 fungoid#s)) OR ((sezary W0 syndrome)) OR retinoblastoma* OR pheochromocytoma* OR nephroblastoma* OR choriocarcinoma* OR ((pleuropulmonary W0 blastoma#)) OR glioblastoma* OR glioma* OR astrocytoma* OR ependymoma* OR medulloblastoma* OR meningioma* OR craniopharyngioma* OR myelodysplastic OR myeloproliferative OR macroglobulinemi* OR macroglobulinaemi* OR pineoblastoma* OR oncol* OR cyst OR tumo#r*)

S2 TI TI (cancer* OR carcinoma* OR adenocarcinoma* OR hepatocarcinoma* OR carcinosarcoma* OR sarcoma* OR histiocytoma* OR fibrosarcoma* OR osteosarcoma* OR chondrosarcoma* OR lymphosarcoma* OR rhabdomyosarcoma* OR leukemi* OR leukaemi* OR erythroleukem* OR erythroleukaem* OR lymphoma* OR melanoma* OR hodgkin* OR 'multiple myeloma' OR mesothelioma* OR neoplas* OR malignan* OR metastas* OR carcinoid* OR neuroblastoma* OR ((mycosis W0 fungoid#s)) OR ((sezary W0 syndrome)) OR retinoblastoma* OR pheochromocytoma* OR nephroblastoma* OR choriocarcinoma* OR ((pleuropulmonary W0 blastoma#)) OR glioblastoma* OR glioma* OR astrocytoma* OR ependymoma* OR medulloblastoma* OR meningioma* OR craniopharyngioma* OR myelodysplastic OR myeloproliferative OR macroglobulinemi* OR macroglobulinaemi* OR pineoblastoma* OR oncol* OR cyst OR tumo#r*)

S1 (MH "Neoplasms+")

5—Cochrane

#1 MeSH descriptor: [Neoplasms] explode all trees

#2 cancer*:ti,ab,kw OR carcinoma*:ti,ab,kw OR adenocarcinoma*:ti,ab,kw OR hepatocarcinoma*:ti,ab,kw OR carcinosarcoma*:ti,ab,kw OR sarcoma*:ti,ab,kw OR histiocytoma*:ti,ab,kw OR fibrosarcoma*:ti,ab,kw OR osteosarcoma*:ti,ab,kw OR chondrosarcoma*:ti,ab,kw OR lymphosarcoma*:ti,ab,kw OR rhabdomyosarcoma*:ti,ab,kw OR leukemi*:ti,ab,kw OR leukaemi*:ti,ab,kw OR erythroleukem*:ti,ab,kw OR erythroleukaem*:ti,ab,kw OR lymphoma*:ti,ab,kw OR melanoma*:ti,ab,kw OR hodgkin*:ti,ab,kw OR 'multiple myeloma':ti,ab,kw OR mesothelioma*:ti,ab,kw OR neoplas*:ti,ab,kw OR malignan*:ti,ab,kw OR metastas*:ti,ab,kw OR carcinoid*:ti,ab,kw OR neuroblastoma*:ti,ab,kw OR ((mycosis NEXT fungoid$s):ti,ab,kw) OR ((sezary NEXT syndrome):ti,ab,kw) OR retinoblastoma*:ti,ab,kw OR pheochromocytoma*:ti,ab,kw OR nephroblastoma*:ti,ab,kw OR choriocarcinoma*:ti,ab,kw OR ((pleuropulmonary NEXT blastoma$):ti,ab,kw) OR glioblastoma*:ti,ab,kw OR glioma*:ti,ab,kw OR astrocytoma*:ti,ab,kw OR ependymoma*:ti,ab,kw OR medulloblastoma*:ti,ab,kw OR meningioma*:ti,ab,kw OR craniopharyngioma*:ti,ab,kw OR myelodysplastic:ti,ab,kw OR myeloproliferative:ti,ab,kw OR macroglobulinemi*:ti,ab,kw OR macroglobulinaemi*:ti,ab,kw OR pineoblastoma*:ti,ab,kw OR oncol*:ti,ab,kw OR cyst:ti,ab,kw OR tumo$r*:ti,ab,kw

#3 #1 or #2

#4 MeSH descriptor: [Calcinosis] this term only

#5 MeSH descriptor: [Hypercalcemia] this term only

#6 calcinos*:ti,ab OR hypercalcemi*:ti,ab

#7 #4 or #5 or #6

#8 #3 and #7

#9 hhm:ti,ab OR loh:ti,ab

#10 #8 or #9

#11 MeSH descriptor: [Attitude to Health] explode all trees

#12 MeSH descriptor: [Patient Participation] this term only

#13 MeSH descriptor: [Patient Preference] this term only

#14 MeSH descriptor: [Cost-Benefit Analysis] this term only

#15 MeSH descriptor: [Decision Making] explode all trees

#16 (patient*:ti,ab,kw OR user*:ti,ab,kw OR famil*:ti,ab,kw OR customer*:ti,ab,kw OR consumer*:ti,ab,kw OR client*:ti,ab,kw OR women:ti,ab,kw OR woman:ti,ab,kw OR men:ti,ab,kw OR man:ti,ab,kw OR individual?:ti,ab,kw)

#17 #15 AND #16

#18 ((decision NEAR/3 (board* OR tool* OR analy* OR support)):ti,ab,kw) OR equit*:ti,ab,kw OR equality:ti,ab,kw OR feasib*:ti,ab,kw OR perspective*:ti,ab,kw OR cost:ti,ab,kw OR resource*:ti,ab,kw OR ((balance NEAR/1 sect*):ti,ab,kw) OR ((discrete* NEAR/1 choice*):ti,ab,kw) OR (((decision* NEAR/1 mak*):ti,ab,kw) AND (patient*:ti,ab,kw OR user*:ti,ab,kw OR famil*:ti,ab,kw OR customer*:ti,ab,kw OR consumer*:ti,ab,kw OR client*:ti,ab,kw OR women:ti,ab,kw OR woman:ti,ab,kw OR men:ti,ab,kw OR man:ti,ab,kw OR individual*:ti,ab,kw))

#19 (preference*:ti,ab,kw OR choice*:ti,ab,kw OR valu*:ti,ab,kw OR expectation$:ti,ab,kw OR attitude*:ti,ab,kw OR acceptab*:ti,ab,kw OR knowledg*:ti,ab,kw) OR sustain*:ti,ab,kw OR barrier*:ti,ab,kw OR access*:ti,ab,kw OR implement*:ti,ab,kw OR inequit*:ti,ab,kw OR disparit*:ti,ab,kw OR inequalit*:ti,ab,kw OR income:ti,ab,kw OR socioeconomic*:ti,ab,kw OR gamble:ti,ab,kw OR utilit*:ti,ab,kw OR ((health NEXT stat*):ti,ab,kw) OR adhere*:ti,ab,kw OR ((quality NEAR/2 life):ti,ab,kw) OR qol:ti,ab,kw OR willing*:ti,ab,kw OR burden*:ti,ab,kw OR satisf*:ti,ab,kw OR opinion*:ti,ab,kw OR (((patient* OR user* OR health*) NEAR/3 (participat* OR perce*)):ti,ab,kw)

#20 #11 OR #12 OR #13 OR #14 OR #17 OR #18 OR #19

#21 #10 AND #20

#22 #10 AND #20 with Cochrane Library publication date Between Apr 2010 and Apr 2020

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Appendix 1B. Second independent search strategy

Medline (OVID)

1 hypercalcemia.mp. or exp Hypercalcemia/
2 cancer.mp. or exp Neoplasms/
3 1 and 2
4 patient preference.mp. or exp Patient Preference/
5 decision making.mp. or exp Decision Making/
6 values.mp. or exp Social Values/
7 cost.mp. or exp "Costs and Cost Analysis"/
8 "Delivery of Health Care"/ or Health Equity/ or equity.mp. or Health Services Accessibility/ or Health Status Disparities/
9 trade off.mp.
10 standard gamble.mp. or Attitude to Health/
11 patient satisfaction.mp. or exp Patient Satisfaction/
12 feasibility.mp.
13 accessability.mp.
14 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15 3 and 14
16 remove duplicates from 15

Appendix 2. Patient questionnaire to obtain information about values, preferences, feasibility, acceptability, and other factors needed for developing a recommendation

What regimen is used to treat your hypercalcemia of malignancy?

- Bisphosphonates intravenously every 4 weeks
- Denosumab injection subcutaneously every 4 weeks
- ther: ……

What regimen do you prefer?

- Bisphosphonates intravenously every 4 weeks
- Denosumab injection subcutaneously every 4 weeks
- No preference
- Other: ……

Why? ……
Where do you receive your treatment?

- Hospital
- Home
- Nursing home/long-term care facility
- Other: ……

Who administers your treatment?

- Health care worker
- Pharmacists
- Family member
- Self-administration
- Other: ……

What setting of treatment administration do you prefer?

- Hospital
- Administration at home by a health care worker
- Administration at home by a family member
- Self-administration at home
- Other: ……

Acceptability:
Do you feel that your treatment regimen is acceptable in terms of benefits, side effects, costs and implementation?

- Yes
- No: why? …….

Feasibility:
What potential barriers or challenges do you face when receiving your treatment?

- Time of administration
- Intervals of treatments
- Mode of drug delivery (oral, injection, etc.)
- Distance to center for administration
- Cost
- Other: ……

Values and preferences:
Which of following issues are most important to you when choosing a specific treatment regimen for hypercalcemia of malignancy?

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	Not important					Important			Critical
Correction of hypercalcemia	1	2	3	4	5	6	7	8	9
Time to normal calcium levels	1	2	3	4	5	6	7	8	9
Duration of normal calcium levels	1	2	3	4	5	6	7	8	9
Effect on mortality	1	2	3	4	5	6	7	8	9
Effect on quality of life	1	2	3	4	5	6	7	8	9
Side effects	1	2	3	4	5	6	7	8	9
Mode of administration	1	2	3	4	5	6	7	8	9
Time of treatment administration	1	2	3	4	5	6	7	8	9
Setting of treatment administration (home vs hospital)	1	2	3	4	5	6	7	8	9
Physician's opinion	1	2	3	4	5	6	7	8	9
Cost	1	2	3	4	5	6	7	8	9
Insurance Coverage	1	2	3	4	5	6	7	8	9

Appendix 3. List of excluded articles

Author	Year	Title	Reason for exclusion
Boisaubin	1991	Hypercalcemia of advanced malignancy: Decision making and the quality of death	Not outcomes of interest
Hall	1993	Update on the medical treatment of hypercalcemia of malignancy	No full text available
Hillner	2000	Pamidronate in prevention of bone complications in metastatic breast cancer: A cost-effectiveness analysis	Not population of interest
Gammon	2003	Zoledronic acid vs pamidronate for the prevention of hypercalcemia of malignancy or bone metastases in hospital outpatients: time analysis and economic implications	Not population of interest
Ando	2011	Hypercalcemia in our palliative care unit-whether to intervene intensively or watch warmly-analysis by the quantified QOL score (IDAS)	No full text available
Azam	2014	Physicians' attitude toward recurrent hypercalcemia in terminally ill cancer patients	No full text available
De las Penas	2014	Burden of skeletal-related events in prostate cancer: unmet need in pain improvement	Not outcomes of interest
Assmann	2014	Quality of life and health care consumption in primary care patients with elevated serum calcium concentrations in a prospective, case control, study	Not population of interest
Zdradzinski	2015	Impact of frailty and sociodemographic factors on hospital admission from an emergency department observation unit	Not population of interest
Adam	2016	Hypercalcemia, symptoms, differential diagnostics and treatment, or importance of calcium investigation [Czech]	Not English
Sadiq	2017	Hypercalcemia	Not outcomes of interest
Tella	2018	Racial disparities in health care utilization costs and mortality in hypercalcemia of malignancy (HCM): national inpatient sample registry based study	No full text available
Asonitis	2019	Diagnosis, pathophysiology and management of hypercalcemia in malignancy: a review of the literature	Not outcomes of interest
Allison	2019	Calcitonin stewardship strategies	Not outcomes of interest
Skoch	2020	Management of urgent medical conditions at the end of life	Not outcomes of interest
O'Callaghan	2021	Treatment of malignancy-associated hypercalcemia with cinacalcet: a paradigm shift	Not outcomes of interest
Alzahrani	2021	Perceptions around bone-modifying agent use in patients with bone metastases from breast and castration resistant prostate cancer: a patient survey	Not population of interest
Baral	2021	Impact and predictors of readmission in hypercalcemia of malignancy: findings of a nationwide analysis	No full text available
Marte	2021	Evaluation of a pharmacy-driven calcitonin protocol for treating hypercalcemia in hospitalized patients: a multisite study	Not population of interest

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Appendix 4A. Risk of bias and quality assessment of cross-sectional surveys using the CLARITY tool[1]

Is the source population representative of the population of interest?	Is the response rate adequate?	Is there little missing data?	Is the survey clinically sensible?	Validity of the survey instrument?	Overall quality
Definitely yes	Probably yes	Probably yes	Definitely yes	Definitely no	Good
Mori et al (2016) (12)	*"nationwide cross-sectional survey, in which a self-reported questionnaire was mailed to eligible physicians in 2004"*	Response rate 50%	*"The percentage does not add up to 100% due to missing data"*	Face validity was confirmed in a pilot test	*"Due to lack of validated instruments, we developed the questionnaire through discussions"*
Shimada et al (2015) (13)	*"nationwide cross-sectional survey, in which a self-reported questionnaire was mailed to eligible physicians in 2004"*	Response rate 50%	Not mentioned	Face validity was confirmed in a pilot test.	*"Due to lack of validated instruments, we developed the questionnaire through discussions"*

[1]The CLARITY tool does not provide a guide for overall quality scores. We therefore developed the overall score as follows: 4 or 5 domains with ratings of definitely/probably yes = good quality; 3 domains with ratings of definitely/probably yes = fair quality; 2 or fewer domains with ratings of definitely/probably yes = poor quality.

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Appendix 4B. Risk of bias and quality assessment of observational studies using the Newcastle–Ottawa tool

	Selection				Comparability	Outcome			Overall quality
	Representativeness exposed cohort	Selection of nonexposed cohort	Ascertainment of exposure	Absence of outcome of interest at start of study	Comparability of cohorts on the basis of design or analysis	Assessment of outcome	Follow-up enough for outcome to occur	Adequacy of follow up of cohorts	
Marr et al. (2010) (14)	No star *"Selected group […] patients referred to the community based palliative care consult team (physicians and nurses) of the Calgary Regional Palliative Care Team"*	NA No comparison group	* Record linkage	*	NA	* Record linkage	* All subjects accounted for in analysis	*	Fair
Khan et al. (2021) (15)	* Somewhat representative *"This was a retrospective, observational cohort study performed at a 664-bed, tertiary care academic medical center"*	* Same community as non-exposed	* Record linkage	*	No star	* Outcomes obtained from medical records	* Time-line 48 hours	No star No statement	Fair

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Appendix 5A. Hypercalcemia of malignancy treatment (zoledronate, pamidronate, and denosumab) cost per country

Country	Drug[1]	Type	Name (Country manufacturer)	Dose	Cost/dose[2]	N doses/ year	Cost/year[2]
Lebanon	Zoledronate	Brand	Zometa (Austria)	4 mg/5 mL	170 USD	12	2040 USD
			Dromezon (Lebanon)		73 USD		876 USD
		Generic	Zoledronic acid Fresenius Kabi (Austria)		28 USD		336 USD
			Zoledronic acid Hikma (Jordan/Portugal)		147 USD		1768 USD
	Denosumab	Brand	Xgeva	120 mg SC	404 USD	12	4848 USD
KSA	Zoledronate	Brand	(Zometa) Zoledronic acid monohydrate, Novartis (Switzerland)	5 mg	434 USD	12	5208 USD
	Denosumab	Brand	(Prolia) Denosumab, Amgen (Netherland)	60 mg	290 USD	24	6960 USD
Russia	Zoledronate	Brand	Zometa (Austria)	4 mg/5 mL	95 USD[3]	12	1145 USD
				4 mg/100 mL	65 USD[3]		778 USD
			Zolerix (Russia)	0.8 mg/mL, 5 mL	79 USD[3]		943 USD
		Generic	Resorba (Russia)	4 mg/5 mL	95 USD[3]		1136 USD
				4 mg/100 mL	99 USD[3]		1190 USD
				4 mg lyophilized powder	97 USD[3]		1169 USD
			Metastasol (Russia)	4 mg/100 mL	55 USD[3]		659 USD
			Resoclastin (Russia)	4 mg/5 mL	77 USD[3]		924 USD
			Zolendronic acid (Russia)	0.8 mg/mL, 5 mL	67 USD[3]		802 USD
			Targesol (Russia)	0.8 mg/mL, 5 mL	55 USD[3]		659 USD
			Zolendronic-Rus4 (Russia)	4 mg lyophilized powder	79 USD[3]		943 USD
			Veroclast (Russia)	4 mg/5 mL	79 USD[3]		943 USD
				4 mg lyophilized powder	55 USD[3]		659 USD
			Zolera (Russia)	4 mg lyophilized powder	79 USD[3]		943 USD
			Zolendronate-Teva (Croatia)	4 mg/5 mL	33 USD[3]		396 USD
			Zolendronic acid (Republic of Belarus)	4 mg lyophilized powder	69 USD[3]		828 USD
			Zoledronate-Teva (Israel)	4 mg/5 mL	51 USD[3]		608 USD
	Denosumab	Brand	Xgeva	120 mg SC	241 USD[3]	12	2891 USD
		Generic	Pomegara (Switzerland)	9 mg/mL, 10 mL	160 USD[4]	12	1916 USD
	Ibadronate	Brand	Bandronate[5] (Germany)	2 mg/2 mL	73 USD[4]	12	880 USD
			Bandronate[5] (Germany)	6 mg/6 mL	158 USD	12	1892 USD
Singapore[6]	Zoledronate	Brand	Aclasta	5 mg/100 mL	418 USD	12	5016 USD
	Denosumab	Brand	Xgeva	120 mg/1.7 mL	429 USD	12	5148 USD
	Pamidronate	Generic	Pamidronate disodium	90 mg/10 mL	130 USD	12	1 560 USD
India	Zoledronate	Brand	Zoldria (Cipla)	4 mg	43.22 USD	12	518.64 USD
			Zolasta (Intas)	4 mg	49.54 USD	12	594.48 USD
		Generic	Zoldonat (Natco)	4 mg	21 USD	12	252 USD
			Dronicad (Cadila)	4 mg	29.27 USD	12	351.24 USD
	Denosumab	Brand	Xgeva	120 mg	356.92 USD	12	4283.04 USD
	Pamidronate	Brand	Bonapam (Alkem)	90 mg	71.91 USD	12	862.92 USD
		Generic	Pamidria (Cipla)	90 mg	21 USD	12	252 USD
Italy	Zoledronate	Brand	Aclasta (Novartis Pharma; Sandoz)	5 mg/100 mL	638 USD	12	7655 USD
		Generic	Aurobindo Pharma	5 mg/100 mL	Ex-factory price: 154 USD Retail price: 254 USD	12	Ex-factory price: 1850 USD Retail price: 3054 USD
	Denosumab	Brand	X-geva (Amgen)	120 g	550 USD	12	6599 USD

(*continued*)

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Appendix 5A. Continued

Country	Drug[1]	Type	Name (Country manufacturer)	Dose	Cost/dose[2]	N doses/ year	Cost/year[2]
France	Zoledronate	Brand	Zometa (Novartis Pharma SAS)	4 mg/100 mL	Manufacturer price excluding tax: 103 USD Retail price: 120 USD	12	Manufacturer price excluding tax: 1236 USD Retail price: 1440 USD
		Generic	Acide zolédronique (Medipha, Pfizer, Mylan, Medac)	4 mg/100 mL	Manufacturer price excluding tax: 103 USD Retail price: 120 USD		Manufacturer price excluding tax: 1236 USD Retail price: 1440 USD
			Acide zolédronique (Mylan)	4 mg/5 mL	Manufacturer price excluding tax: 121 USD Retail price: 140 USD		Manufacturer price excluding tax: 1452 USD Retail price: 1680 USD
	Denosumab	Brand	Xgeva (Amgen)	120 mg SC	Manufacturer price excluding tax: 286 USD Retail price: 329 USD	12	Manufacturer price excluding tax: 3432 USD Retail price: 3948 USD
UK	Zoledronate	Brand	Zometa (Novartis), Zoledronic acid (Pfizer)	4 mg/100 mL	NHS indicative price: 242 USD	12	NHS indicative price: 2904 USD
			Zometa (Novartis), Zoledronic acid (Pfizer)	4 mg/5 mL	NHS indicative price: 242 USD		NHS indicative price: 2904 USD
			Aclasta (Novartis)	5 mg/100 mL	NHS indicative price: 352 USD		NHS indicative price: 4224 USD
			Zoledronic acid (Pfizer)		NHS indicative price: 302 USD		NHS indicative price: 3624 USD
		Generic	Zoledronic acid (Dr Reddy's laboratories)	4 mg/100 mL	NHS indicative price: 242 USD		NHS indicative price: 2904 USD
			Zoledronic acid (Seacross)		NHS indicative price: 118 USD		NHS indicative price: 1416 USD
			Zoledronic acid (Accord Healthcare)	4 mg/5 mL	NHS indicative price: 230 USD		NHS indicative price: 2760 USD
			Zoledronic acid (Dr Reddy's laboratories)		NHS indicative price: 242 USD		NHS indicative price: 2904 USD
			Zoledronic acid (Fresenius Kabi)		NHS indicative price: 324 USD		NHS indicative price: 3888 USD
			Zoledronic acid (Mylan)		NHS indicative price: 206 USD		NHS indicative price: 2472 USD
			Zoledronic acid (Seacross)		NHS indicative price: 42 USD		NHS indicative price: 504 USD
			Zoledronic acid (A A H Pharmaceuticals)		NHS indicative price: 14 USD		NHS indicative price: 168 USD
			Zoledronic acid (Dr Reddy's laboratories)	5 mg/100 mL	NHS indicative price: 352 USD		NHS indicative price: 4224 USD
			Zoledronic acid (Seacross)		NHS indicative price: 118 USD		NHS indicative price: 1416 USD
			Zoledronic acid (Sun Pharmaceutical Industries Europe B.V.)		NHS indicative price: 370 USD		NHS indicative price: 4440 USD
	Denosumab	Brand	Xgeva (Amgen)	120 mg SC	NHS indicative price: 430 USD	12	NHS indicative price: 5160 USD
	Pamidronate	Brand	Pamidronate disodium (Pfizer)	90 mg/10 mL	NHS indicative price: 237 USD	12	NHS indicative price: 2844 USD
		Generic	Pamidronate disodium (medac)	90 mg/30 mL	NHS indicative price: 229 USD		NHS indicative price: 2748 USD
			Pamidronate disodium (Wockhardt)	90 mg/9 mL	NHS indicative price: 237 USD		NHS indicative price: 2844 USD
USA	Zoledronate	Brand	Zometa (USA) (Novartis)	4 mg/100 mL	1107 USD	12	13284 USD
		Generic	Zoledronic acid (USA) Athenex		57 USD		684 USD
			Zoledronic acid (USA) Hospira		72 USD		868 USD
			Zoledronic acid (USA) Sagent:		216 USD		2592 USD
	Denosumab	Brand	Xgeva (USA)	120 mg SC	2,823 USD	12	33874 USD
	Pamidronate	Brand	Aredia (USA) (Novartis)	90 mg/10 mL	840 USD	12	10075 USD
		Generic	Pamidronate (USA) Areva Pharma	90 mg/10 mL	70 USD	12	845 USD
Brazil[7]	Zoledronate	Brand	Zometa (Novartis)	4 mg/100 mL	132 USD	12	1584 USD
			Zolibbs (libbs)	4 mg/100 mL	186 USD		2232 USD
		Generic	Zoledronic Acid (Cristalia Quimico)	4 mg/5 mL	52 USD		624 USD
			Zoledronic Acid (Sun do Brasil)	4 mg lyophilized powder	52 USD		624 USD
	Denosumab	Brand	XGEVA (AMGEN)	120 mg SC	182 USD	12	2184 USD
	Pamidronate	Brand	Pamidrom (Cristalia Quimico)	60 mg lyophilized powder	100 USD	12	1200 USD

(*continued*)

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Appendix 5A. Continued

Country	Drug[1]	Type	Name (Country manufacturer)	Dose	Cost/dose[2]	N doses/ year	Cost/year[2]
			Pamidrom (Cristalia Quimico)	90 mg lyophilized powder	154 USD	12	1848 USD
			FAULDPAMI (Libbs)	90 mg/10 mL	149 USD		1788 USD
		Generic	Pamidronate (Eurofarma)	90 mg lyophilized powder	110 USD		1320 USD
Australia[8]	Zoledronate	Brand	APO-Zoledronic acid DBL Zoledronic acid DEZTRON Zometa	4 mg/5 mL	64 USD (the patient would only pay 30 USD or 5 USD)	12	764 USD (the patient would only pay 371 or 60 USD)
	Denosumab	Brand	Xgeva	120 mg SC	385 USD (the patient would only pay 30 USD or 5 USD)	12	4619 USD (the patient would only pay 371 or 60 USD)
	Pamidronate	Brands	Pamisol	90 mg/10 mL	62 USD (the patient would only pay 30 USD or 5 USD)	12	749 USD (the patient would only pay 371 or 60 USD)

[1]Medications for hypercalcemia of malignancy including:
Zoledronic acid 4 mg intravenously over ≥15 minutes every 4 weeks.
Pamidronate 90 mg intravenously over ≥2 hours every 4 weeks.
Denosumab 120 mg subcutaneously every 4 weeks
Doses as per up to date and FDA websites
[2]Lebanon: conversion: 1 USD = 1500 LBP, data collected by Aya Bassatne, MD, from the MOPH website (moph.gov.lb).
KSA: conversion 1USD = 3.75 SAR, data collected by Youssef El Saleh, MD, past president Saudi osteoporosis society and endocrinologist.
Russia: conversion 1USD = 73.88 RUB, data collected by Tatiana Karonova, MD, PhD, Member of HPTH International workshop, Task force 6, chaired by Ghada and Claudio from the Russian Pharmaceutical website (pharmindex.ru).
Singapore: conversion 1USD = 1.33 SGD, Manju Chandran, MD, IOF member.
India: conversion 1 USD = 72.58 INR, data collected by Ambrish Mithal, MD, Endocrine Society laureate Excellence in Endocrinology award, member of HPTH TF6.
Italy and France: conversion 1 USD = 0.83€, data collected by Mirella Hage, MD, PhD, faculty at a University Hospital in Paris INSERM from the ministry of health database (France) and Claudio Marcocci, MD (Italy).
UK: Conversion 1 USD = 0.72 £, data collected by Dr. Richard Eastell and Dr. Marian Schini, University of Sheffield from the NICE British National Formulary (BNF).
Brazil: conversion 1 USD = 5.38 BRL, data collected by Barbara Silva, MD, PhD from http://antigo.anvisa.gov.br/consulta-lista-de-preco-de-medicamento.
Australia: conversion 1USD = 1.33 AUD, data collected by Farah Andary, MD.
USA: data collected by Mathew Drake, MD, PhD.
[3]Medications are supplied by the government free of charge as vital treatment. The price is regulated by the government.
[4]Medications that are not included in the list of vital treatment. Can be bought by the patients. The prices (medium price in Russia) are gathered from pharmindex.ru, the Russian Pharmaceutical website.
[5]Dose of ibandronic acid depends of serum calcium level.
[6]Costs in Singapore differ by hospital setting (public vs private). Cost represented in the table is as per the Singapore General Hospital.
[7]Maximum cost allowed for government purchases, without taxes, as determined by The Brazilian Health Regulatory Agency (ANVISA). Taxes in Brazil will vary from 12% to 20%.
[8]30 USD is the price the patients pay, if they have a concession card (pensioner, commonwealth, seniors, health card care or DVA cards) they will pay 5 USD. For concession card holders when the spending amount reaches 234 USD they would apply for "safety net" and get the medication for free. For all other patients if they reach spending amount of 1100 USD they would apply for "safety net" and will start paying 5 USD for each medication.

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Appendix 5B. Hypercalcemia of malignancy treatment (cinacalcet) cost per country

Country	Drug	Type	Name (country manufacturer)	Dose	Cost/dose[1]
Lebanon	Cinacalcet	Brand	Cencipral	30 mg	142 USD (cost/28 tabs)
				60 mg	262 USD (cost/28 tabs)
			Mimpara	30 mg	226 USD (cost/28 tabs)
				60 mg	560 USD (cost/28 tabs)
				90 mg	437 USD (cost/28 tabs)
KSA	Cinacalcet	Brand	PATHEON (Canada)	30 mg	189 USD (cost/28 tabs)
			Marketed by (Amgen)	60 mg	365 USD (cost/28 tabs)
				90 mg	522 USD (cost/28 tabs)
Russia[2]	Cinacalcet	Brand	Mimpara	30 mg	133 USD (cost/28 tabs)
		Generic	Cinacalcet (Russia)	30 mg	94 USD (cost/28 tabs)
				60 mg	187 USD (cost/28 tabs)
				90 mg	281 USD (cost/28 tabs)
			Cinacalcet-TL (Russia)	30 mg	94 USD (cost/28 tabs)
			Cinacalcet (India)	30 mg	100 USD (cost/30 tabs)
				60 mg	200 USD (cost/30 tabs)
				90 mg	287 USD (cost/30 tabs)
				60 mg	196 USD (cost/28 tabs)
				90 mg	295 USD (cost/28 tabs)
India	Cinacalcet	Brand	Mimcipar (Panacea)	30 mg	8.2 USD (per 10 tablets)
			Pth (Intas)	30 mg	8.7 USD (per 10 tablets)
			Pth (Intas)	60 mg	16.5 USD (per 10 tablets)
		Generic	Setz (Dr. Reddy's)	30 mg	6.8 USD (per 10 tablets)
Italy	Cinacalcet	Brand	Mimpara (Amgen)	30 mg	326 USD
				60 mg	603 USD
				90 mg	904 USD
		Generic	Aurobindo Pharma-Biovalley Investment – Aristo Pharma and many others	30 mg	171 USD
				60 mg	317 USD
				90 mg	475 USD
France	Cinacalcet	Brand	Mimpara (Amgen)	30 mg	Manufacturer price excluding tax: 196 USD (cost/28 tabs) Retail price: 227 USD
				60 mg	Manufacturer price excluding tax: 363 USD (cost/28 tabs) Retail price: 417 USD
				90 mg	Manufacturer price excluding tax: 544 USD (cost/28 tabs) Retail price: 624 USD
		Generic	Cinacalcet (Accord, Arrow, Biogaran, EG, Evolugen, Mylan, Teva, Zentiva)	30 mg	Manufacturer price excluding tax: 79 USD (cost/28 tabs) Retail price: 98 USD
				60 mg	Manufacturer price excluding tax: 145 USD (cost/28 tabs) Retail price: 169 USD
				90 mg	Manufacturer price excluding tax: 218 USD (cost/28 tabs) Retail price: 270 USD
UK	Cinacalcet	Brand	Mimpara (Amgen)	30 mg	NHS indicative price: 175 USD (cost/28 tabs)
				60 mg	NHS indicative price: 322 USD (cost/28 tabs)
				90 mg	NHS indicative price: 483 USD (cost/28 tabs)
		Generic	Cinacalcet (A A H Pharmaceuticals, Mylan)	30 mg	NHS indicative price: 148 USD (cost/28 tabs)
			Cinacalcet (Accord Healthcare)		NHS indicative price: 21 USD (cost/28 tabs)
			Cinacalcet (Zentiva)		NHS indicative price: 41 USD (cost/28 tabs)
			Cinacalcet (Alliance Healthcare, Dr Reddy's Laboratories, Genus Pharmaceuticals, Macleods, Torrent)		NHS indicative price: 175 USD (cost/28 tabs)
			Cinacalcet (A A H Pharmaceuticals, Mylan)	60 mg	NHS indicative price: 274 USD (cost/28 tabs)
			Cinacalcet (Accord Healthcare)		NHS indicative price: 39 USD (cost/28 tabs)
			Cinacalcet (Zentiva)		NHS indicative price: 77 USD (cost/28 tabs)
			Cinacalcet (Dr Reddy's Laboratories, Genus Pharmaceuticals, Macleods, Torrent)		NHS indicative price: 322 USD (cost/28 tabs)
			Cincacalcet (Alliance Healthcare)		NHS indicative price: 266 USD (cost/28 tabs)

(*continued*)

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Appendix 5B. Continued

Country	Drug	Type	Name (country manufacturer)	Dose	Cost/dose[1]
			Cinacalcet (A A H Pharmaceuticals, Mylan)	90 mg	NHS indicative price: 411 USD (cost/28 tabs)
			Cinacalcet (Accord Healthcare)		NHS indicative price: 59 USD (cost/28 tabs)
			Cinacalcet (Zentiva)		NHS indicative price: 115 USD (cost/28 tabs)
			Cinacalcet (Dr Reddy's Laboratories, Genus Pharmaceuticals, Macleods, Torrent)		NHS indicative price: 483 USD (cost/28 tabs)
			Cinacalcet (Alliance Healthcare)		NHS indicative price: 398 USD (cost/28 tabs)
USA	Cinacalcet	Brand	Sensipar (Accord Healthcare)	30 mg	858 USD (cost/28 tabs)
				60 mg	1,716 USD (cost/28 tabs)
				90 mg	2,576 USD (cost/28 tabs)
		Generic	Cinacalcet (Exelan)	30 mg	357 USD (cost/28 tabs)
				60 mg	714 USD (cost/28 tabs)
				90 mg	1,071 USD (cost/28 tabs)
Brazil[3]	Cinacalcet[4]	Brand	Mimpara (Amgen)	30 mg	87 USD (cost/30 tabs)
				60 mg	171 USD (cost/30 tabs)
				90 mg	245 USD (cost/30 tabs)
			Calt (Cristalia Quimico)	30 mg	87 USD (Cost/30 tabs)
				60 mg	171 USD (cost/30 tabs)
		Generic	Cinacalcet (EMS)	30 mg	57 USD (cost/30 tabs)
				60 mg	111 USD (cost/30 tabs)
Australia[5]	Cinacalcet	Brand	Pharmacor Cinacalcet	30 mg	65 USD/56 tabs (the patient would only pay 30 USD or 5 USD)
				60 mg	130 USD/56 tabs (the patient would only pay 30 USD or 5 USD)
				90 mg	195 USD/56 tabs (the patient would only pay 30 USD or 5 USD)

[1]Lebanon: conversion: 1 USD = 1500 LBP, data collected by Aya Bassatne, MD, from the MOPH website (moph.gov.lb).
KSA: conversion 1 USD = 3.75 SAR, data collected by Youssef El Saleh, MD past president Saudi osteoporosis society and endocrinologist.
Russia: conversion 1USD = 73.88 RUB, data collected by Tatiana Karonova, MD, PhD, Member of HPTH International workshop, Task force 6, chaired by Ghada and Claudio from the Russian Pharmaceutical website (pharmindex.ru).
Singapore: conversion 1USD = 1.33 SGD, Manju Chandran, MD, IOF member.
India: conversion 1 USD = 72.58 INR, data collected by Ambrish Mithal, MD, Endocrine Society laureate Excellence in Endocrinology award, member of HPTH TF6.
Italy and France: conversion 1 USD = 0.83€, data collected by Mirella Hage, MD, PhD, faculty at a University Hospital in Paris INSERM from the ministry of health database (France) and Claudio Marcocci, MD (Italy).
UK: Conversion 1 USD = 0.72£, data collected by Dr. Richard Eastell and Dr. Marian Schini, University of Sheffield from the NICE British National Formulary (BNF).
Brazil: conversion 1 USD = 5.38 BRL, data collected by Barbara Silva, MD, PhD from http://antigo.anvisa.gov.br/consulta-lista-de-preco-de-medicamento.
Australia: conversion 1 USD = 1.33 AUD, data collected by Farah Andary, MD.
USA: data collected by Mathew Drake, MD, PhD.
[2]In Russia Cinacalcet is not registered for treatment of hypercalcemia of malignancy.
[3]Maximum cost allowed for government purchases, without taxes, as determined by The Brazilian Health Regulatory Agency (ANVISA). Taxes in Brazil will vary from 12% to 20%.
[4]Cinacalcet is not used in Brazil for the treatment of malignancy hypercalcemia, unless in cases of parathyroid carcinoma.
[5]30 USD is the price the patients pay, if they have a concession card (pensioner, commonwealth, seniors, health card care or DVA cards) they will pay 5 USD. For concession card holders when the spending amount reaches 234 USD they would apply for "safety net" and get the medication for free. For all other patients if they reach spending amount of 1100 USD they would apply for "safety net" and will start paying 5 USD for each medication.

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