

# Patients' values and other decisional factors regarding treatment of hypercalcemia of malignancy: A Systematic Review Protocol

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## Protocol

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## **Abstract**

## **Background**

Hypercalcemia of malignancy is the second most common cause of hypercalcemia and is associated with significant morbidity and mortality. Several treatment options are available including pharmacological therapy with bisphosphonates, denosumab, glucocorticoids, and calcimimetics, as well as conventional therapy with hydration and possibly calcitonin. While guidelines have previously considered treatment effects, no guideline has yet considered a range of contextual factors impacting recommendations for the management.

## **Objective**

The aim of this study is to summarize the available evidence on important decisional factors for the development of guidelines for the treatment of hypercalcemia of malignancy. These include patient's values and preferences, cost, acceptability, feasibility, and equity.

## **Methods/Design:**

This is a systematic review of observational studies, case series, trials, reviews and qualitative studies involving treatment of adult patients with hypercalcemia of malignancy. We developed and executed two independent search strategies using five databases: Pubmed, Medline (OVID), Embase.com, CINAHL (EBSCO) and Cochrane, and reviewed their combined output. Two reviewers screened titles and abstracts and full texts and will implement data abstraction from relevant studies independently and in duplicate. The outcomes of interest are the decisional factors that influence drug selection, with possible subgroup analyses by drug class or etiology of hypercalcemia of malignancy. We will present the data collected in a narrative and thematic approach.

## **Discussion**

This systematic review will identify important treatment decisional factors, and will assist guidelines panels, physicians and patients to decide on therapeutic options based on the current evidence.

## **Background**

Hypercalcemia affects 1 to 2% of the general population. Hypercalcemia of malignancy (HCM) is considered the second most common cause of hypercalcemia, after hyperparathyroidism in adults (1). In fact, one third of cancer patients will eventually experience hypercalcemia with the most common causes being breast cancer, lung cancer and multiple myeloma (2, 3). HCM arises due to four main mechanisms: humoral secretion of parathyroid hormone related peptide (PTHrP) accounts for over 80% of cases and

occurs most commonly in breast cancer and squamous cell carcinoma of the lung, head and neck, and the kidney, local osteolytic release of calcium, known as local osteolytic hypercalcemia (LOH), such as seen with multiple myeloma and some breast cancers, high levels of calcitriol (1,25-dihydroxyvitamin D) such as noted in leukemias, HTLV1, and some lymphomas, or secretion of the native parathyroid hormone (PTH) from a carcinoma, or ectopic PTH secretion by some cancers including neuroendocrine tumors (Table 1) (4, 5). These include tumors in the head and neck, thorax, gastrointestinal system, or genito-urinary system (6). Hypercalcemia can be classified into mild, moderate or severe. Although mild hypercalcemia can be asymptomatic, moderate and severe hypercalcemia can be associated with a wide range of symptoms from polyuria, polydipsia, dehydration, nephrolithiasis, and muscle weakness all the way to renal failure, lethargy, coma, and cardiac arrest (4). Although not very common, HCM is associated with a longer hospital stay and greater mortality risk when compared to cancer patients without HCM (7). In fact, 50% of patients with HCM may die within a month (7, 8). Therefore, treatment is of utmost importance.

Treatment of hypercalcemia of malignancy constitutes of hydration, calciuresis and inhibition of bone resorption (4, 8), regardless of the operating mechanism (Table 2). The efficacy of different bisphosphonates was investigated in several clinical trials to determine their value in HCM treatments (9–12). This lead to the replacement of calcitonin and glucocorticoids in the treatment of HCM by bisphosphonates which are now the preferred treatment options (8). Pamidronate was approved in 1991, and zoledronic acid was approved in 2000 for the treatment of HCM. However, results pooled from Phase III trials have shown zoledronic acid to be more potent than pamidronate with faster normalization of calcium levels, longer duration of calcium control and a higher response rate (13). In 2014, Denosumab a RANKL inhibitor has been approved for the treatment of HCM refractory to bisphosphonates with significant efficacy (2, 14). Approval was based on a therapy-open label one arm phase II multicenter trial of 21 patients (15). Both bisphosphonates and denosumab are also approved to reduce skeletal related events in patients with solid tumors and multiple myeloma (16). Hypercalcemia associated with parathyroid carcinoma has been more difficult to treat. Common medical approaches such as calcitonin, glucocorticoids and bisphosphonates have failed (17, 18). Cinacalcet, a calcimimetic was found to be effective in lowering calcium levels and maintaining them in patients with parathyroid carcinoma (19), while glucocorticoids are commonly used for the treatment of myeloma, and cancers associated with elevated calcitriol levels.

When patients and clinicians choose among the many treatments of HCM, consideration of benefits (effectiveness evidence) and harms about patient-important outcomes are usually the main driver of the decision (20). This is currently assessed by a systematic review of benefits and harms of currently used drugs to treat the various diseases associated with hypercalcemia of malignancy. However, many other factors also affect the choice of treatment and are important for shared-decision making. The GRADE Working Group has developed an Evidence-to-Decision (EtD) framework for the assessment of factors that should complement evidence on the benefits and harms when guideline groups make recommendations. In fact, some of the treatment options involved in hypercalcemia of malignancy may be costly reaching up to 620\$ per dose, inconvenient and time consuming for some patients who are not

able to travel to a nearby hospital for infusion (21). All of these factors should be taken into consideration when deciding on a treatment option to deliver the best care possible.

## **Study Objectives**

The evidence to decision framework from the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Working Group (Evidence to Decision, EtD) describes five other such factors: patient's values, costs and resources, feasibility, acceptability, and equity (22). We initially used a search strategy of Epistemonikos that included key words and MESH terms capturing the key decisional factors, in the treatment of hypercalcemia of malignancy, screening the database for applicable systematic reviews (23). We were unable to find any relevant publication on the topic (Appendix 1). Therefore, and to better inform the recommendations to be made by the Endocrine Society in its Clinical Practice Guidelines on Treatment of Hypercalcemia of Malignancy, we decided to conduct a rigorous meta-narrative systematic review to summarize the best available evidence about these decisional factors.

## **Methods / Design**

Due to the wide availability of different treatment options for hypercalcemia of malignancy, the aim of this systematic review is to identify important contextual and decisional factors that affect choices for therapies of hypercalcemia of malignancy in adult patients.

### **Information sources and search strategy**

We conducted a comprehensive search using the following online databases: Medline (OVID), Pubmed, Embase.com, the Cochrane Library and CINAHL (EBSCO). The research team developed a search strategy for each data base using MESH terms and keywords related to malignancy, hypercalcemia and factors guiding therapy decision such as patients' values and preferences, acceptability, equity, cost-effectiveness and feasibility, that was applied to adults, and limited to the last 10 years. We did not include any language restrictions. The strategy was reviewed and verified by the medical librarian at the American university of Beirut (LH), and two methodologists, at the Mayo Evidence Based Center (MHM) and the McMaster University (TP) (Appendix 2A). We also developed and executed another independent search using Medline, without any time limit, and the results were combined with the original search (Appendix 2B). We also plan to identify papers by hand searching references from the included studies.

### **Eligibility criteria**

We included observational studies, trials, reviews and qualitative studies conducted in adult patients ( $\geq$  18 years of age) with hypercalcemia of malignancy. We included studies reporting on pharmacological therapy such as bisphosphonates, denosumab, diuretics, calcitonin, and calcimimetics as well as conservative management including hydration, avoiding calcium rich diet and vitamin D supplementation. We excluded case reports, studies conducted in the pediatric population or in patients

with hypercalcemia from a condition unrelated to malignancy for example parathyroid disease, Familial Hypocalciuric Hypercalcemia (FHH), vitamin D intoxication, and side effects of medications.

## Outcomes

Our outcomes of interest are EtD factors:

- Patients or physicians values (how patients or physicians value each outcome in terms of its importance to their context and daily life)
- Cost and resources (cost effectiveness, actual charges, out of pocket costs)
- Acceptability (of treatment options and their method of administration)
- Feasibility (of the intervention as it relates to the health care environment)
- Equity (whether the intervention would exacerbate health disparities or create inequities)

We will exclude studies with inadequate outcome measurement or reporting.

## Study Selection

We downloaded the literature search results into Covidence software (Covidence 2020) (24). We developed and pilot tested a screening sheet for title and abstract and another for the full texts (Appendix 3), based on our exclusion and inclusion criteria of individual studies. We performed a calibration exercise to familiarize the reviewers with the screening process.

All reviewers (AB, MR, TP, MHM, GEHF) contributed to pilot testing the screening at the title and abstract level for 100 citations. Two reviewers (AB, MR) then independently screened the remaining titles and abstracts using the screening sheet developed (Appendix 3A). We retrieved the full texts of all included citations. Two reviewers (AB, MR) screened these records independently and in duplicate using the full text screening guide (Appendix 3B). All disagreements throughout the screening process were resolved through discussion or with the help of a third reviewer as needed (TP, MHM, GEHF). All reasons for exclusion were recorded.

## Data collection and abstraction

Following the full text screening, two reviewers (AB, MR) will complete data abstraction independently and in duplicate using standardized data collection tables (Appendix 4). We will implement a calibration exercise to familiarize the reviewers with the process. If any disagreement occurs during data abstraction, it will be resolved through discussion or with the help of a third reviewer as needed (TP, MHM, GEHF). We will contact the authors in case of remaining disagreements and uncertainties. We will extract the first author's name, date of publication and the study design, and will collect data on the characteristics, methodology and results of each of the included studies (Appendix 4). In case of any missing data, we will contact the authors of the individual studies to obtain the relevant information.

## Data Synthesis

The methodological quality of the included studies will be evaluated using tools appropriate for each study design, including randomized trials, cohort and case control studies, case series, and qualitative research (25-30).

Data will be analyzed thematically and presented narratively. Two independent reviewers will identify themes from each article until saturation and reach consensus on how the themes would converge into unique. A third reviewer will adjudicate when consensus is not reached.

The certainty of evidence derived from the studies will be evaluated using the GRADE-CERQual approach which appraises qualitative research domains analogous to GRADE. This approach focuses on the methodological limitations of the studies, coherence, adequacy, and relevance of the findings (30).

## Discussion

Treatment of hypercalcemia of malignancy is sometimes challenging due to the extensive variety of options available and wide range of benefits and harms. This systematic review will provide data on important decisional factors, which will help shape future guidelines on the management of hypercalcemia of malignancy. This study will also allow physicians and patients to decide on a therapy option based on the current evidence.

To our knowledge, this is the first systematic review conducted in hypercalcemia of malignancy to detect important decisional factors such as patient's values, costs and resources, feasibility, acceptability, and equity. The strength of this systematic review stands in its novelty, and extensive and systematic search of the literature. However, some limitations might be encountered due to the scarcity of available data and lack of reporting of our outcomes of interest.

## Abbreviations

HCM: Hypercalcemia of malignancy, PTHrP: Parathyroid hormone related peptide, LOH: local osteolytic hypercalcemia, PTH: Parathyroid Hormone, EtD: evidence to decision, GRADE: Grading of Recommendations, Assessment, Development and Evaluation, FHH: Familial Hypocalciuric Hypercalcemia.

## Declarations

Ethical Approval and Consent to participate: Not applicable

Consent for publication: Not applicable

Availability of supporting data: Not applicable

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## Tables

**Table 1:** Mechanisms of hypercalcemia of malignancy and examples of their associated malignancies

Mechanism of hypercalcemia of malignancy	Associated malignancies
Local Osteolytic hypercalcemia	Multiple myeloma Breast carcinoma Leukemia Lymphoma
Humoral Hypercalcemia of Malignancy: secretion of parathyroid hormone related peptide (PTHrP)	Squamous cell carcinoma Renal carcinoma Bladder carcinoma Breast carcinoma Ovarian carcinoma Prostate carcinoma Colorectal carcinoma Non-Hodgkin lymphoma Leukemia
Tumors associated with elevated calcitriol levels	Lymphoma Lymphomatoid granulomatosis/angiocentric lymphoma  Ovarian dysgerminoma
PTH secreting tumors:  Parathyroid Carcinoma  or Ectopic secretion of parathyroid hormone (PTH)	Ovarian carcinoma Lung carcinoma Neuroectodermal tumor Neuroendocrine tumor  Thyroid papillary carcinoma Rhabdomyosarcoma Pancreatic carcinoma

**Table 2:** Hypercalcemia of malignancy treatment options

Intervention	Mode of action	Examples
<b>Conventional therapy</b>		
Isotonic saline hydration	Restores intravascular volume Increases urinary calcium excretion	0.9% NaCl
<b>Pharmacological therapy</b>		
Bisphosphonates	Inhibit bone resorption	IV bisphosphonates: Pamidronate  Zoledronate  Oral bisphosphonates: Clodronate Ibandronate Etidronate
Denosumab	Inhibits bone resorption	-
Calcitonin	Inhibits bone resorption Promotes urinary calcium excretion	-
Glucocorticoids	Decrease intestinal calcium absorption Decrease 1,25-dihydroxyvitamin D production by activated mononuclear cells	Prednisone Methylprednisolone
Calcimimetics	Calcium-sensing receptor agonist, reduces PTH synthesis and secretion	Cinacalcet

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [PRISMAPchecklist.doc](#)
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- Appendix2.docx
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