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Values and other decisional factors regarding treatment of hypercalcaemia of malignancy: a systematic review protocol

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ABSTRACT

Introduction Hypercalcaemia of malignancy (HCM) is the second most common cause of hypercalcaemia 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. The aim of this study was to summarise the available evidence on important decisional factors for the development of guidelines for the treatment of HCM. These include patient's values and preferences, cost, acceptability, feasibility and equity.

Methods and analysis This protocol is registered in PROSPERO (registration number: CRD42021264371). This is a systematic review of observational studies, case series, trials, reviews and qualitative studies involving treatment of adult patients with HCM. We will develop and execute two independent search strategies using five databases: PubMed, Medline (OVID), Embase.com, CINAHL (EBSCO) and Cochrane, and review their combined output. Two reviewers will screen 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 summaries by drug class or aetiology of HCM. We will present the data collected in a narrative and thematic approach.

Ethics and dissemination Ethical approval is not applicable for our study, since we will only collect data from available literature. This systematic review will be submitted to a peer-reviewed journal when completed.

Strengths and limitations of this study

- Our systematic review would investigate important decisional factors regarding treatment of hypercalcaemia of malignancy.
- It would evaluate predictors of values and preferences of patients and of physicians impacting such therapeutic decisions.
- It would systematically capture studies reporting on cost, acceptability, feasibility and equity of various treatments.
- It may be limited by the potential scarcity of identified studies and limited reporting on outcomes of interest.
- Some of our findings might be outdated with regard to cost, and not generalisable across different populations.

INTRODUCTION

Hypercalcaemia affects 1%–2% of the general population. Hypercalcaemia of malignancy (HCM) is considered the second most common cause of hypercalcaemia, after hyperparathyroidism in adults.[1] In fact, one-third of patients with cancer will eventually experience hypercalcaemia, with the most common causes being breast cancer, lung cancer and multiple myeloma.[2 3] HCM arises due to four main mechanisms: (1) humoral secretion of parathyroid hormone-related peptide 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; (2) local osteolytic release of calcium, known as local osteolytic hypercalcaemia, such as seen with multiple myeloma and some breast cancers; (3) 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 (4) ectopic PTH secretion by some cancers including neuroendocrine tumours (table 1).[4 5] These include tumours in the head and neck, thorax, gastrointestinal system or genitourinary system.[6] Hypercalcaemia can be classified into mild, moderate or severe. Although mild hypercalcaemia can be asymptomatic, moderate and severe hypercalcemia can be associated with a wide range

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Table 1 Mechanisms of hypercalcaemia of malignancy and examples of their associated malignancies

Mechanism of hypercalcaemia of malignancy	Associated malignancies
Local osteolytic hypercalcaemia	Multiple myeloma Breast carcinoma Leukaemia Lymphoma
Humoral hypercalcaemia of malignancy: secretion of parathyroid hormone-related peptide	Squamous cell carcinoma Renal carcinoma Bladder carcinoma Breast carcinoma Ovarian carcinoma Prostate carcinoma Colorectal carcinoma Non-Hodgkin's lymphoma Leukaemia
Tumours associated with elevated calcitriol levels	Lymphoma Lymphomatoid granulomatosis/ angiocentric lymphoma Ovarian dysgerminoma
PTH secreting tumours: parathyroid carcinoma or ectopic secretion of PTH	Ovarian carcinoma Lung carcinoma Neuroectodermal tumour Neuroendocrine tumour Thyroid papillary carcinoma Rhabdomyosarcoma Pancreatic carcinoma

PTH, parathyroid hormone.

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 with patients with cancer without HCM.[7] In fact, 50% of patients with HCM may die within a month.[8] Therefore, treatment is of utmost importance.

Treatment of HCM constitutes of hydration, calciuresis and inhibition of bone resorption,[4 9] 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.[10–13] This led to the replacement of calcitonin and glucocorticoids in the treatment of HCM by bisphosphonates which are now the preferred treatment options.[9] 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 normalisation of calcium levels, longer duration of calcium control and a higher response rate.[14] In 2014, denosumab, a receptor activator of nuclear factor kappa-B ligand inhibitor, has been approved for the treatment of HCM refractory to bisphosphonates with significant efficacy.[2 15] Approval was based on a therapy open-label one-arm phase II multicentre trial of 21 patients.[16] Both bisphosphonates and denosumab are also approved to reduce skeletal-related events in patients with solid tumours and multiple myeloma.[17] Hypercalcaemia associated with parathyroid carcinoma has been more difficult to treat. Common medical approaches such as calcitonin, glucocorticoids and bisphosphonates have failed.[18 19] Cinacalcet, a calcimimetic, was found to be effective in lowering calcium levels and maintaining them in patients with parathyroid carcinoma,[20] while glucocorticoids are commonly used for the treatment of myeloma and cancers associated with elevated calcitriol levels.

When patients and clinicians choose among the several treatments of HCM, consideration of benefits (effectiveness evidence) and harms about patient-important outcomes is usually the main driver of the decision.[21] This is currently assessed by a systematic review of benefits and harms of currently used drugs to treat the various diseases associated with HCM. However, many other factors also affect the choice of treatment and are important for

Table 2 Hypercalcaemia of malignancy treatment options

Intervention	Mode of action	Examples
Conventional therapy		
Isotonic saline hydration	Restores intravascular volume Increases urinary calcium excretion	0.9% NaCl
Pharmacological therapy		
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 Methylprednisone
Calcimimetics	Calcium-sensing receptor agonist, reduces PTH synthesis and secretion	Cinacalcet

IV, intravenous; NaCl, sodium chloride; PTH, parathyroid hormone.

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shared decision-making. The Grading of Recommendations, Assessment, Development and Evaluation (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. The EtD framework from the GRADE Working Group (EtD) describes five other such factors: patient's values, costs and resources, feasibility, acceptability and equity.[22] 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 summarise the best available evidence about the above described decisional factors.

Study objectives

The objective of this systematic review was to summarise the available evidence on important decisional factors including physicians' and patients' values and preferences, cost, acceptability, feasibility and equity, for the development of guidelines for the treatment of HCM.

METHODS

Due to the wide availability of different treatment options for HCM, the aim of this systematic review was to identify important contextual and decisional factors that affect choices for therapies of HCM in adult patients. This protocol is reported as per the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) checklist.[23] This protocol is registered in PROSPERO (registration number: CRD42021264371).

Information sources and search strategy

We initially used a search strategy through Epistemonikos database to identify any prior systematic review that addressed factors related to decisional frameworks (online supplemental material 1A) in the treatment of HCM.[24] We were unable to find any relevant publication on the topic (online supplemental material 1B). We will therefore conduct 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 database using MESH terms and keywords related to malignancy, hypercalcaemia and factors guiding therapy decision such as patients' values and preferences, acceptability, equity, cost-effectiveness and feasibility, which was applied to adults. The concept and therefore literature regarding decisional frameworks is relatively new, we therefore limited our search to the last 10 years. With no 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 Centre (MHM) and the McMaster University (TP) (online supplemental material 2A). We also developed another independent search using Medline, without any time limit (online supplemental material 2B). We will execute both searches up to 15 March 2021, and combine their outputs. We will test and use these two search strategies with varying sensitivity and specificity, which were developed independently by two coauthors to obtain better coverage of the literature. We will also try to identify papers by hand searching references from the included studies and studies that have cited the included studies.

Eligibility criteria

We will include observational studies (cohort, cross-sectional and case–control studies), trials, reviews and qualitative studies conducted in adult patients (≥18 years of age) with HCM. We will include 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 will exclude case reports, studies conducted in the paediatric population or in patients with hypercalcaemia from a condition unrelated to malignancy, for example, parathyroid disease, familial hypocalciuric hypercalcaemia, vitamin D intoxication and side effects of medications.

Outcomes

Our outcomes of interest are EtD factors:

- Patients' or physicians' values (how patients'amilial hypocalciuric hypercalcaemia 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 healthcare 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 will download the literature search results into Covidence software.[25] We developed a screening sheet for title and abstract and another for the full texts (3) based on our exclusion and inclusion criteria of individual studies. We will perform a calibration exercise to familiarise the reviewers with the screening process.

All reviewers (AB, MR, TP, MHM, GE-HF) will contribute to pilot testing the screening at the title and abstract level for 100 citations. Two reviewers (AB, MR) will then screen the remaining titles and abstracts using the screening sheet developed independently and in duplicate (online supplemental material 3A). We will retrieve the full texts of all included citations. Two reviewers (AB, MR) will screen these records independently and in duplicate using the full-text screening guide (online supplemental material

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3B). All disagreements throughout the screening process will be resolved through discussion or with the help of a third reviewer as needed (TP, MHM, GE-HF). All reasons for exclusion will be recorded. We will measure the agreement between the two reviewers (AB, MR) at each screening step using the Cohen's kappa statistic.

Data collection and abstraction

Following the full-text screening, two reviewers (AB, MR) will complete data abstraction independently and in duplicate using standardised data collection tables (online supplemental material 4). We will implement a calibration exercise to familiarise the reviewers with the process. We will resolve any disagreements through discussion or with the help of a third reviewer as needed (TP, MHM, GE-HF). 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 (online supplemental material 4).

Quality assessment of included studies

The methodological quality of the included studies will be evaluated using tools appropriate for each study design, including randomised trials, cohort and case–control studies, case series and qualitative research.[26–31] Quality assessment will be done independently and in duplicate.

To assess the quality of any identified RCTs (Randomized Controlled Trials), we will use the Cochrane Risk of Bias tool which assesses the following domains: bias due to sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data and selective outcome reporting.[27] To assess the quality of observational studies, we will use the New Castle-Ottawa quality assessment scale assessing the following categories: selection, comparability and outcome.[28] For case series, we will assess four domains: selection, ascertainment, causality and reporting.[29] Finally, for qualitative articles, we will use the CASP (Critical Appraisal Skills Programme) appraisal checklist.[30]

Data synthesis

Data will be analysed thematically and presented narratively. Two independent reviewers will identify themes from each article that can map to a concept in the EtD framework. For example, a theme about whether patients prefer a certain treatment characteristic can map to the acceptability domain in the framework. Consensus among the two reviewers about themes is reached via discussion. We will seek a state of saturation in which the two reviewers are reasonably assured that further data collection would yield similar results. The next step after saturation is to confirm emerging themes and conclusions. 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 four domains: methodological limitations, coherence, adequacy and relevance.[31] The overall assessment of confidence in the review findings will be based on the assessment of these individual domains.

The methodological limitations domain is assessed in individual studies based on the appropriate design, conduct, and data collection and analysis methods.[32] The coherence domain assesses how clear and consistent the individual studies data are with the overall results of the review.[33] The adequacy domain assesses the extent of details and available information provided in the review.[34] Finally, the relevance domain assesses the extent to which the gathered individual data answers the review's objectives and questions.[35]

Patient and public involvement

No patient involved.

DISCUSSION

Treatment of HCM 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 HCM. 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 HCM 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.

Ethics and dissemination

Ethical approval is not applicable for our study, since we will only collect data from available literature. This systematic review will be submitted to a peer-reviewed journal when completed.

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REFERENCES

1 Sadiq NM, Naganathan S, Badireddy M. *Hypercalcemia*. StatPearls: Treasure Island (FL): StatPearls Publishing LLC, 2020.
2 Thosani S, Hu MI. Denosumab: a new agent in the management of hypercalcemia of malignancy. *Future Oncol* 2015;11:2865–71.
3 Goldner W. Cancer-related hypercalcemia. *J Oncol Pract* 2016;12:426–32.
4 Asonitis N, Angelousi A, Zafeiris C, *et al*. Diagnosis, pathophysiology and management of hypercalcemia in malignancy: a review of the literature. *Horm Metab Res* 2019;51:770–8.
5 Chisholm MA, Mulloy AL, Taylor AT. Acute management of cancer-related hypercalcemia. *Ann Pharmacother* 1996;30:507–13.
6 Kandil E, Noureldine S, Khalek MA, *et al*. Ectopic secretion of parathyroid hormone in a neuroendocrine tumor: a case report and review of the literature. *Int J Clin Exp Med* 2011;4:234–40.
7 Bhandari S, Kumar R, Tripathi P, *et al*. Outcomes of hypercalcemia of malignancy in patients with solid cancer: a national inpatient analysis. *Med Oncol* 2019;36:90.
8 Ralston SH, Gallacher SJ, Patel U, *et al*. Cancer-associated hypercalcemia: morbidity and mortality. clinical experience in 126 treated patients. *Ann Intern Med* 1990;112:499–504.
9 Wright JD, Tergas AI, Ananth CV, *et al*. Quality and outcomes of treatment of hypercalcemia of malignancy. *Cancer Invest* 2015;33:331–9.
10 Singer FR, Ritch PS, Lad TE, *et al*. Treatment of hypercalcemia of malignancy with intravenous etidronate. a controlled, multicenter study. the hypercalcemia study group. *Arch Intern Med* 1991;151:471–6.
11 Kawada K, Minami H, Okabe K, *et al*. A multicenter and open label clinical trial of zoledronic acid 4 Mg in patients with hypercalcemia of malignancy. *Jpn J Clin Oncol* 2005;35:28–33.
12 Pecherstorfer M, Steinhauer EU, Rizzoli R, *et al*. Efficacy and safety of ibandronate in the treatment of hypercalcemia of malignancy: a randomized multicentric comparison to pamidronate. *Support Care Cancer* 2003;11:539–47.
13 Nussbaum SR, Younger J, Vandepol CJ, *et al*. Single-dose intravenous therapy with pamidronate for the treatment of hypercalcemia of malignancy: comparison of 30-, 60-, and 90-mg dosages. *Am J Med* 1993;95:297–304.
14 Major P, Lortholary A, Hon J, *et al*. Zoledronic acid is superior to pamidronate in the treatment of hypercalcemia of malignancy: a pooled analysis of two randomized, controlled clinical trials. *J Clin Oncol* 2001;19:558–67.
15 Dellay B, Groth M. Emergency management of malignancy-associated hypercalcemia. *Adv Emerg Nurs J* 2016;38:15–25.
16 Hu MI, Glezerman IG, Leboulleux S, *et al*. Denosumab for treatment of hypercalcemia of malignancy. *J Clin Endocrinol Metab* 2014;99:3144–52.
17 Terpos E, Ntanasis-Stathopoulos I, Dimopoulos MA. Myeloma bone disease: from biology findings to treatment approaches. *Blood* 2019;133:1534–9.
18 de Papp AE, Kinder B, LiVolsi V, *et al*. Parathyroid carcinoma arising from parathyroid hyperplasia: autoinfarction following intravenous treatment with pamidronate. *Am J Med* 1994;97:399–400.
19 Mann K. Oral biphosphonate therapy in metastatic parathyroid carcinoma. *Lancet* 1985;1:101–2.
20 Silverberg SJ, Rubin MR, Faiman C, *et al*. Cinacalcet hydrochloride reduces the serum calcium concentration in inoperable parathyroid carcinoma. *J Clin Endocrinol Metab* 2007;92:3803–8.
21 Gandhi GY, Murad MH, Fujiyoshi A, *et al*. Patient-important outcomes in registered diabetes trials. *JAMA* 2008;299:2543–9.
22 Alonso-Coello P, Schünemann HJ, Moberg J, *et al*. Grade evidence to decision (ETD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 1: introduction. *BMJ* 2016:i2016.
23 Moher D, Shamseer L, Clarke M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4.
24 foundation E. Epistemonikos. Available: https://www.epistemonikos.org/
25 Covidence. Covidence, 2020. Available: www.covidence.org
26 Viswanathan M, Patnode CD, Berkman ND, *et al*. Recommendations for assessing the risk of bias in systematic reviews of health-care interventions. *J Clin Epidemiol* 2018;97:26–34.
27 Rob 2: a revised Cochrane risk-of-bias tool for randomized trials, 2019. Available: https://methods.cochrane.org/bias/resources/rob-2-revised-cochrane-risk-bias-tool-randomized-trials
28 Wells BS, D GA, O'Connell JP, Welch V, *et al*. The newcastle-ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses, 200. Available: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
29 Murad MH, Sultan S, Haffar S, *et al*. Methodological quality and synthesis of case series and case reports. *BMJ Evid Based Med* 2018;23:60–3.
30 Casp checklist, 2018. Available: https://casp-uk.net/wp-content/uploads/2018/01/CASP-Qualitative-Checklist-2018.pdf
31 Cerqual G. Confidence in the evidence from reviews of qualitative research, 2018. Available: https://www.cerqual.org/
32 Munthe-Kaas H, Bohren MA, Glenton C, *et al*. Applying grade-cerqual to qualitative evidence synthesis findings—paper 3: how to assess methodological limitations. *Implementation Science* 2018;13:9.
33 Colvin CJ, Garside R, Wainwright M, *et al*. Applying grade-cerqual to qualitative evidence synthesis findings—paper 4: how to assess coherence. *Implementation Science* 2018;13:13.
34 Glenton C, Carlsen B, Lewin S, *et al*. Applying grade-cerqual to qualitative evidence synthesis findings-paper 5: how to assess adequacy of data. *Implement Sci* 2018;13:14.
35 Noyes J, Booth A, Lewin S, *et al*. Applying grade-cerqual to qualitative evidence synthesis findings-paper 6: how to assess relevance of the data. *Implement Sci* 2018;13:4.

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