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FULL PAPER

A review of cancer-related hypercalcemia: Pathophysiology, current treatments, and future directions

Arif Nur Muhammad Ansori[a,b,c,d,e] |Muhammad Hermawan Widyananda[f] |Yulanda Antonius[g] |Ahmad Affan Ali Murtadlo[c,h] |Viol Dhea Kharisma[c,h] |Putu Angga Wiradana[i] |Sukma Sahadewa[j] |Fara Disa Durry[k] |Nikolai Maksimiuk[l] |Maksim Rebezov[m,n] |Rahadian Zainul[o,p,*]

[a]*Postgraduate School, Universitas Airlangga, Surabaya, Indonesia*
[b]*Uttaranchal Institute of Pharmaceutical Sciences, Uttaranchal University, Dehradun, India*
[c]*Division of Research and Development, Jalan Tengah, Surabaya, Indonesia*
[d]*European Virus Bioinformatics Center, Jena, Germany*
[e]*The Indonesian Society for Bioinformatics and Biodiversity, Jakarta, Indonesia*
[f]*Faculty of Mathematics and Natural Sciences, Universitas Brawijaya, Malang, Indonesia*
[g]*Faculty of Biotechnology, University of Surabaya, Surabaya, Indonesia*
[h]*Department of Biology, Faculty of Science and Technology, Universitas Airlangga, Surabaya, Indonesia*
[i]*Research Group of Biological Health, Study Program of Biology, Faculty of Health and Science, Universitas Dhyana Pura, Bali, Indonesia*
[j]*Faculty of Medicine, Universitas Wijaya Kusuma Surabaya, Surabaya, Indonesia*
[k]*Faculty of Medicine, Universitas Pembangunan Nasional "Veteran" Jawa Timur, Surabaya, Indonesia*
[l]*Institute of Medical Education, Yaroslav-the-Wise Novgorod State University, Velikiy Novgorod, Russian Federation*
[m]*Department of Scientific Research, V.M. Gorbatov Federal Research Center for Food Systems, Moscow, Russian Federation*
[n]*Faculty of Biotechnology and Food Engineering, Ural State Agrarian University, Yekaterinburg, Russian Federation*
[o]*Department of Chemistry, Faculty of Mathematics and Natural Sciences, Universitas Negeri Padang, Padang, Indonesia*
[p]*Center for Advanced Material Processing, Artificial Intelligence, and Biophysic Informatics (CAMPBIOTICS), Universitas Negeri Padang, Padang, Indonesia*

***Corresponding Author:**
Rahadian Zainul
Email:rahadianzmsiphd@fmipa.unp.ac.id
Tel.: + 62 812-6138-53

Cancer-related hypercalcemia is a common metabolic complication seen in patients with advanced malignancies, affecting 10-30% of all cancer patients. It is associated with significant morbidity and mortality, highlighting the need for a comprehensive understanding of its pathophysiology and effective treatment strategies. The pathophysiology of cancer-related hypercalcemia involves the dysregulation of calcium homeostasis, primarily through the production of parathyroid hormone-related protein (PTHrP) by malignant cells. Moreover, it may associated to the stimulation of osteoclast activity resulting in increased bone resorption and release of calcium into the bloodstream. In addition, certain tumors can directly stimulate osteoclast activity and cause bone destruction. Dysregulation of renal calcium handling also contributes to hypercalcemia in cancer patients. However, future research directions in cancer-related hypercalcemia aimed to elucidate tumor-specific mechanisms, identify novel therapeutic targets, and develop personalized treatment approaches. Combination therapies, biomarkers, and predictive factors can enhance treatment efficacy and guide clinical decision-making. Furthermore, the focus on supportive care, psychosocial support, and palliative measures is essential to optimize patient comfort and quality of life. Improved imaging techniques, studies in pediatric populations, and investigations into long-term outcomes are also warranted. Advancements in these areas will contribute to better management and outcomes for cancer patients with hypercalcemia.

KEYWORDS

Cancer-related hypercalcemia; cancer biology; medicine; pathophysiology; treatment strategies.

Introduction

Cancer-related hypercalcemia is a common metabolic complication in patients with advanced malignancies [1-3]. Hypercalcemia is characterized by higher-than-normal levels of calcium in the bloodstream, frequently triggered by the disruption of calcium balance due to malignant tumors. It is estimated that 10-30% of all cancer patients experience hypercalcemia, with a higher incidence seen in those with advanced-stage disease [4,5]. The presence of hypercalcemia in cancer patients has been associated with significant morbidity and mortality, highlighting the importance of understanding its pathophysiology and identifying effective treatment strategies [6,7].

The pathophysiology of cancer-related hypercalcemia involves intricate interactions between tumor cells, bone metabolism, and renal calcium handling [8]. A key mechanism involves malignant cells producing parathyroid hormone-related protein (PTHrP) [9-11]. PTHrP acts as a potent stimulator of osteoclasts, leading to increased bone resorption and subsequent release of calcium into the bloodstream [12]. Furthermore, certain tumors possess the ability to directly stimulate osteoclast activity through the secretion of cytokines and growth factors, exacerbating bone destruction and calcium release. The abnormal handling of calcium by the kidneys, particularly through increased reabsorption in the renal tubules, is another factor that contributes to the onset of hypercalcemia in cancer patients [13].

Clinical manifestations of cancer-related hypercalcemia can vary widely and are influenced by the degree of hypercalcemia [1]. Common symptoms include fatigue, anorexia, nausea, constipation, and cognitive impairment. Severe hypercalcemia may result in cardiac arrhythmias and renal impairment [14]. The timely recognition and management of hypercalcemia are crucial to prevent complications and improve patient outcomes. Therefore, it is essential to explore potential treatment options that target both the underlying causes of hypercalcemia and the associated symptoms.

Pathophysiology

Cancer-related hypercalcemia is a complex condition that arises from various pathophysiological mechanisms. One key contributor is the production of parathyroid hormone-related protein (PTHrP) by cancer cells [1,15]. PTHrP shares structural homology with parathyroid hormone (PTH) and can stimulate osteoclast activity, leading to bone resorption and subsequent release of calcium into the bloodstream [12,16]. This process is particularly prevalent in tumors of the lung, breast, and multiple myeloma. Moreover, PTHrP can interfere with renal calcium excretion, further exacerbating hypercalcemia [9].

Besides PTHrP, cancer-related hypercalcemia can result from the direct stimulation of osteoclast activity by tumor-produced factors, independent of PTHrP. These factors include cytokines, growth factors, and chemokines released by tumor cells, which activate osteoclasts and promote bone resorption [13,17]. Tumors that commonly exhibit this mechanism include those derived from squamous cell carcinomas, renal cell carcinomas, and hematologic malignancies [14,18-19]. The osteoclast-mediated bone destruction releases calcium into the bloodstream, leading to hypercalcemia.

Furthermore, cancer-related hypercalcemia can be caused by bone metastases, which are frequently observed in advanced-stage cancers [20]. The infiltration of tumor cells into bone tissue disrupts the normal balance between bone formation and resorption, favoring increased osteoclast activity and bone destruction [13]. The release of calcium from the damaged bone further contributes to hypercalcemia.

Clinical manifestations

The clinical manifestations of cancer-related hypercalcemia can vary widely, depending on the severity and duration of hypercalcemia, as well as individual patient factors. Mild cases may be asymptomatic or present with nonspecific symptoms such as fatigue, generalized weakness, and malaise. As hypercalcemia progresses, patients may experience anorexia, nausea, and constipation, often due to the effect of elevated calcium levels on the gastrointestinal tract [21]. These symptoms can significantly impact the nutritional status and quality of life of affected individuals.

Cognitive impairment is another common manifestation of cancer-related hypercalcemia, particularly in severe cases. Patients may experience confusion, disorientation, memory deficits, and even delirium [14,20]. These cognitive changes can have a profound impact on the patient's functional abilities and overall well-being. Moreover, cardiac manifestations, including arrhythmias, can occur as a result of the direct effect of elevated calcium levels on cardiac muscle contractility [3]. Severe hypercalcemia can further lead to renal impairment, characterized by polyuria, nocturia, and impaired renal function [21].

The severity of symptoms often correlates with the degree of hypercalcemia. Prompt recognition and management of hypercalcemia are crucial to prevent complications and improve patient outcomes. Identifying and treating the underlying cause of hypercalcemia is essential for effective management.

Diagnostic approach

Based on the clinical perspective, calcium homeostasis is essential and it could be derailed by malignant process in cancer patient (Figure 1). In general, the malignancy of hypercalcemia could be evaluated by measuring PTH and PTH-related protein (PTHrP) [18]. Cancer patient with hypercalcemia could have a higher PTH level or without high PTH level which depend on the malignancy form. Patient with parathyroid cancer commonly had greater level of PTH. Whilst, other malignancy may have disrupted PTH level. Patient with low level of PTH should be addressed for PTHrP level measurement to evaluate the possibility of humoral hypercalcemia. In brief, high level of PTHrP level would be detected within case of humoral hypercalcemia of malignancy. However, if the PTHrP level is normal, a further measurement could be evaluated by measuring the 1,25-dihydroxyvitamin D level and 25-hydroxyvitamin D level to the other form of hypercalcemia [18,22-24].

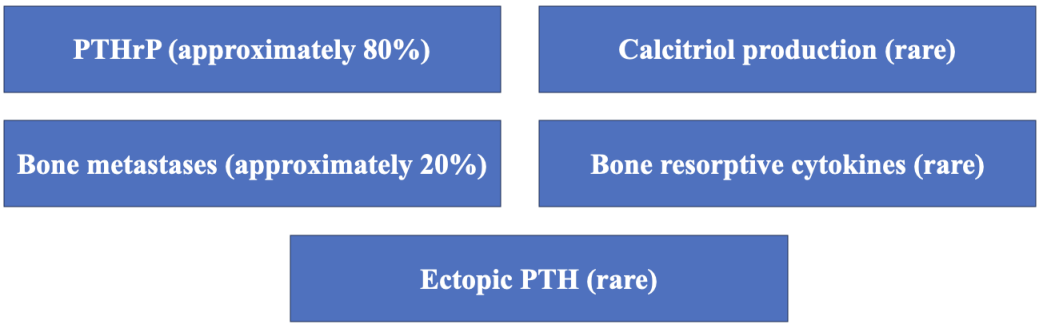

FIGURE 1 The reasons of malignant hypercalcemia

Treatment approach

The management of cancer-related hypercalcemia involves addressing both the underlying cause and the associated symptoms [2]. The primary goals of treatment are to lower serum calcium levels, alleviate symptoms, and improve patient well-being. Initial treatment strategies often involve rehydration with intravenous fluids to enhance renal calcium excretion and promote diuresis [3,5]. This approach helps restore normal hydration and correct electrolyte imbalances.

Bisphosphonates, such as zoledronic acid and pamidronate, are commonly used in the management of cancer-related hypercalcemia. These medications inhibit osteoclast activity and reduce bone resorption, effectively lowering serum calcium levels [14]. Calcitonin, a hormone that suppresses bone resorption, can be administered either intranasally or subcutaneously to provide rapid relief of hypercalcemia symptoms [3]. Glucocorticoids, such as prednisone or dexamethasone, may be also employed as they can suppress the production of parathyroid hormone-related protein (PTHrP) by tumor cells [9]. These treatment modalities aim to target the underlying mechanisms contributing to hypercalcemia.

In cases where initial treatments are ineffective or contraindicated, alternative options may be considered. Denosumab, a monoclonal antibody targeting the receptor activator of nuclear factor-kappa B ligand (RANKL), has shown promising results in managing hypercalcemia associated with solid tumors and multiple myeloma [4]. By inhibiting RANKL, denosumab blocks osteoclast activation and bone resorption. Another potential therapeutic approach is the use of anti-PTHrP antibodies, which specifically target PTHrP and can help normalize calcium levels [26]. These targeted therapies offer additional options for patients with refractory or recurrent hypercalcemia.

Supportive Care and Palliative Measures

In advanced-stage cancer patients with hypercalcemia, supportive care and palliative measures play a crucial role in managing symptoms and improving life quality. Adequate hydration is essential to maintain fluid balance and promote renal calcium excretion. Intravenous fluids, along with oral hydration, should be encouraged to prevent dehydration and further complications [20].

Pain management is another critical aspect of supportive care in cancer-related hypercalcemia. Patients may experience bone pain due to metastatic bone involvement or skeletal complications. Appropriate analgesic medications, such as opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), or adjuvant medications, should be utilized to alleviate pain and enhance patient comfort [24,27-28].

In addition, addressing gastrointestinal symptoms is crucial to optimize nutritional intake and prevent further complications. Antiemetic medications can help manage nausea and vomiting, while laxatives or stool softeners can alleviate constipation [25]. Dietary modifications, such as increasing dietary fiber and fluid intake, may be further recommended to promote regular bowel movements.

Psychosocial support is an integral component of palliative care for cancer patients with hypercalcemia. Patients may experience emotional distress, anxiety, and depression as a result of their condition. Providing access to counseling services, support groups, and resources for coping with the emotional impact of the disease can significantly improve the overall well-being and quality of life for patients and their families [3,29-34].

Future Directions

Despite significant advancements in the understanding and treatment of cancer-

related hypercalcemia, there are several areas that require further exploration and development. Continued research efforts and clinical trials hold the potential to enhance our understanding of the underlying mechanisms and improve treatment strategies for this complex condition [4].

Elucidating tumor-specific mechanisms

Different types of tumors may utilize distinct mechanisms to induce hypercalcemia. Further research is needed to investigate the specific pathways involved in hypercalcemia associated with different cancer types. Understanding these tumor-specific mechanisms can lead to the development of targeted therapies tailored to specific malignancies [3,18].

Novel therapeutic targets

Identifying novel therapeutic targets is essential for expanding treatment options for cancer-related hypercalcemia. In-depth studies are required to explore molecules and signaling pathways involved in bone resorption and calcium homeostasis. Novel inhibitors or modulators of these targets could offer more effective interventions [17].

Personalized approaches

Developing personalized approaches to managing hypercalcemia can optimize treatment outcomes. Molecular profiling of tumors and individual patient characteristics may help identify specific therapeutic targets or predict treatment response. Tailoring treatment plans based on such information can lead to improved efficacy and reduced adverse effects [4].

Combination therapies

Investigating the potential benefits of combination therapies in cancer-related hypercalcemia is warranted. Combinations of different classes of drugs, such as bisphosphonates, targeted therapies, or immunotherapies, may have synergistic effects and improve treatment response rates. Clinical trials exploring these combinations are needed to establish their efficacy and safety [3].

Biomarkers and predictive factors

The identification of reliable biomarkers and predictive factors for cancer-related hypercalcemia can aid in early detection and guide treatment decisions [35,36-37]. Biomarkers associated with tumor-related bone destruction, calcium metabolism, or PTHrP production could serve as diagnostic or prognostic tools [25].

Supportive care and quality of life

Focusing on supportive care and interventions to improve the quality of life of patients with cancer-related hypercalcemia is crucial. Research should explore psychosocial support, pain management strategies, and palliative care interventions to address the physical, emotional, and social aspects of this condition [3].

Comparative effectiveness studies

Comparative effectiveness studies comparing different treatment modalities can help identify the most effective and cost-efficient approaches for managing cancer-related hypercalcemia. These studies can provide valuable insights into the relative benefits and risks of different treatment options [14].

Improved imaging techniques

Developing advanced imaging techniques can aid in the early detection and accurate assessment of hypercalcemia-associated bone metastases. High-resolution imaging modalities, such as positron emission tomography (PET) combined with computed

tomography (CT), may improve diagnostic accuracy and help guide treatment decisions [3].

Pediatric considerations

Research specifically focusing on cancer-related hypercalcemia in pediatric populations is warranted. Children with cancer may present unique challenges and treatment considerations. Studying the underlying mechanisms and developing tailored treatment strategies for pediatric patients can optimize outcomes in this vulnerable population [14].

Long-term outcomes

Long-term outcomes and the impact of hypercalcemia on survivorship and quality of life should be investigated [38]. Understanding the long-term consequences of hypercalcemia and its treatment can guide follow-up care and support for cancer survivors [17].

Conclusion

To sum up, cancer-related hypercalcemia is a complex condition and significant clinical implications. Current treatment strategies focus on addressing the underlying causes, lowering serum calcium levels, and alleviating symptoms. However, future research directions hold promise in improving our understanding and management of this condition. Elucidating tumor-specific mechanisms, identifying novel therapeutic targets, and developing personalized approaches can enhance treatment efficacy. In addition, the focus on supportive care, psychosocial support, and palliative measures is crucial for optimizing patient comfort and quality of life. Continued research efforts and advancements in these areas will contribute to better outcomes for cancer patients with hypercalcemia.

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Authors' Contributions

Conceptualization: Arif Nur Muhammad Ansori, Muhammad Hermawan Widyananda, and Rahardian Zainul; Literature Study: Arif Nur Muhammad Ansori, Muhammad Hermawan Widyananda, and Yulanda Antonius; Formal analysis and investigation: Arif Nur Muhammad Ansori, Ahmad Affan Ali Murtadlo, Viol Dhea Kharisma, Putu Angga Wiradana, Sukma Sahadewa, Fara Disa Durry, Nikolai Maksimiuk, and Maksim Rebezov; Writing original draft: Arif Nur Muhammad Ansori; Funding acquisition: Rahadian Zainul; and Supervision: Rahadian Zainul.

Conflict of Interest

The authors declare no conflict of interest with respect to the study, authorship, and/or publication of this article.

Orcid:

Arif Nur Muhammad Ansori:
https://orcid.org/0000-0002-1279-3904
Muhammad Hermawan Widyananda:
https://orcid.org/0000-0002-0064-8865
Yulanda Antonius:
https://orcid.org/0000-0002-4950-8134
Ahmad Affan Ali Murtadlo:
https://orcid.org/0000-0002-7942-875X
Viol Dhea Kharisma:
https://orcid.org/0000-0001-9060-0429
Putu Angga Wiradana:
https://orcid.org/0000-0002-0139-8781
Sukma Sahadewa:
https://orcid.org/0009-0009-9253-7633
Fara Disa Durry:
https://orcid.org/0009-0003-5589-9746

Maksim Rebezov:
https://orcid.org/0000-0003-0857-5143
Rahadian Zainul:*
https://orcid.org/0000-0002-3740-3597

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