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Pathophysiology and management of hypercalcemia in malignancy

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ABSTRACT

Hypercalcemia is a complication that is often found in patients with malignancy, both blood malignancy and solid tumor malignancy, with a prevalence that can reach 30%. Hypercalcemia caused by malignant conditions is usually characterized by severe clinical manifestations, severe degree, and rapid onset. Hypercalcemia is also one of the markers of poor prognosis in patients with malignancy, often a sign that a malignant condition is in the late stages or is refractory to the treatment given. Management of hypercalcemia in malignancy is based on the underlying pathophysiology. The main pathophysiology is due to humoral hypercalcemia, local osteolytic metastases, increased extrarenal calcitriol, and primary or ectopic PTH secretion. Based on this condition, an understanding of the pathophysiology, clinical manifestations, diagnostic approach, and management of hypercalcemia in malignancy needs to be studied further.

Keywords: Hypercalcemia, Malignancy, Management, Pathophysiology

INTRODUCTION

Hypercalcemia is an electrolyte imbalance with many causes, the most common being primary hyperparathyroidism and malignancies (80–90%). Primary hyperparathyroidism (60%) is the leading cause of hypercalcemia in an outpatient setting, whereas, in the inpatient setting, malignancies are the most common cause (54–65%). Hypercalcemia is defined as an increase in serum calcium of >10.5 mg/dl or >2.5 mmol/l.[1] Among all malignancies, hypercalcemia is reported to have an incidence of 20–30%. Tumor progressiveness correlates with an increased risk of hypercalcemia. In malignancies in which bone metastases have occurred, hypercalcemia has a much higher incidence and is accompanied by skeletal complications (skeletal-related events, SRE).[2] Hypercalcemia occurs most frequently in patients with lung cancer, multiple myeloma, renal cell carcinoma, head and neck squamous cell carcinoma, followed by breast cancer, colorectal cancer, and prostate cancer with the lowest incidence.[2–4]

Hypercalcemia caused by malignancies is mediated through a few mechanisms that could be distinctive in each type of cancer.[2,4] In severe or acute conditions, hypercalcemia could cause severe and life-threatening symptoms. Clinical manifestations that could occur include nausea, vomiting, fatigue, abdominal tenderness, polyuria, a decrease in consciousness, arrhythmias, volume depletion, and renal vasoconstriction.[1]

According to a survival study on solid tumors, it is reported that the median overall survival among patients with hypercalcemia is 40 days (95% CI 33–47). However, this survival rate increased in those undergoing chemotherapy (HR 0.24; 95% CI 0.14–0.4; $p < 0.001$).[5,6] Although some treatments were effective, hypercalcemia is still indicative of poor outcomes in malignancies, especially in the advanced stage or refractory cancer.[7–9] Appropriate treatment of hypercalcemia increases quality of life, decreases morbidity, and provides a fair chance of success for definitive treatment.[10] Due to its high prevalence among tumor patients and its life-threatening clinical manifestations, the pathophysiology, evaluation, and treatments of hypercalcemia in malignancies must be further investigated.

Epidemiology and risk factors

Hypercalcemia prevalence in malignancies reaches 20–30% and increases in patients with metastasis. In early-stage cancers, the prevalence of hypercalcemia is relatively low (1–5%).[7] Hypercalcemia is most prevalent in patients with lung cancer, followed by multiple myeloma, renal cell carcinoma,

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head and neck squamous cell cancer, and least prevalent in breast, colorectal, and prostate cancer in decreasing order.[2–4] Similar to these studies, another research in the United States showed that patients with multiple myeloma have the highest hypercalcemia incidence (7.5–10.2%).[3]

In another study that looked into solid tumors among 306 subjects, the highest prevalence of hypercalcemia was in squamous cell carcinoma (62%) and primary tumor of the head and neck region (28%). The median overall survival of hypercalcemia in malignancies was 40 days (95% CI 33–47). Several factors were associated with a worse prognosis, such as a decrease in consciousness, performance status of >2, albumin <2.5 g/dl, C-reactive protein (CRP) > 30 mg/dl, or a body mass index (BMI) < 18 kg/m^2.[5] Another study investigating the overall survival of patients with hypercalcemia, regardless of the underlying disease, has found a 9.9% mortality in ICU patients and 21.3% mortality in overall hospitalization.[6] O'Callaghan et al. reported that after hypercalcemia diagnosis was confirmed in tumor patients, 50% of them died after 30 days on average, and 75% died within 3 months after.[10] These various studies have found that hypercalcemia in malignancies is a marker for poor prognosis, that is, advanced stage or refractory cancer.[7–9]

There has not been much research in Indonesia that looks into hypercalcemia as a complication from malignancy. A study of hypercalcemia in 40 subjects, 22 of whom had hematological malignancies and 18 of whom had solid tumors, was conducted by Wijaya *et al*. in Hasan Sadikin Hospital in Bandung. The symptoms observed were dehydration (18 subjects), nausea and vomiting (6 subjects), constipation (6 subjects), and decrease of consciousness (4 subjects), while the rest of the subjects were asymptomatic. The study concluded that bisphosphonate administration was beneficial in lowering calcium ions compared to no treatment (0.59; 95% CI 0.01–1.17; p = 0.0001).[11]

Calcium homeostasis

Calcium is a micronutrient that plays a role in biochemical reactions inside our body, including coagulation, bone formation, and muscle contraction. It is collected through intestinal absorption, albeit only 10–20% of them are absorbed while the rest will be secreted in feces. Calcium is then stored in one of two compartments; in bones as hydroxyapatite salt and in plasma as either free calcium ion (45%) or calcium, which binds to carriers (65%), most of which is albumin, followed by phosphate, sulfate, and citric acid.[8] In normal adults, daily calcium levels are maintained in balance. In bones, 280 mg of 1000 g of calcium stored will undergo a turnover, while the other 1000 mg is in circulation.[12,13]

Calcium homeostasis involves a variety of hormones and electrolyte levels, such as calcitonin, 1,25 $(OH)_2D$, parathyroid hormone (PTH), and phosphate and calcium levels. The parathyroid hormone produced by the parathyroid gland will be activated in low calcium levels, that is, <10 mg/dl, due to the stimulation of calcium-sensing cells. Parathyroid hormone production peaks at calcium levels <7.5 mg/dl.[8] Parathyroid hormone helps increase serum calcium levels and decrease phosphate by inducing bone resorption by osteoclast. Besides that, PTH also enhances calcium reabsorption in the Henle loop and distal convoluted tubule of the kidney while decreasing phosphate absorption. Parathyroid hormone also plays a role in the conversion of 25(OH)D (calcidiol) into 1,25$(OH)_2D$ (calcitriol) in the kidney, which is mediated by 1-α-hydroxylase produced in the proximal tubule.[2,8]

Vitamin D also plays a crucial role in calcium metabolism. Vitamin D metabolism starts from its synthetic source in the skin as 7-dehydrocalciferol, converted by ultraviolet (UV) rays to cholecalciferol (vitamin D3). Cholecalciferol then undergoes hydroxylation in the liver at position 25 to 25(OH) D (calcidiol), which is further converted into calcitriol. As the final product, calcitriol is responsible for increasing the absorption of phosphate and calcium in the intestines. After that, calcitriol is deactivated by the enzyme 24,25-hydroxylase in the kidney.[8,12] On the other hand, when serum calcium levels are high, calcitonin, a hormone produced by the thyroid parafollicular C cells, is secreted. Calcitonin will, in turn, decrease the calcium and phosphate absorption in the kidney, as well as decrease bone resorption.[2,8]

The normal calcium metabolism in the bone involves two types of cells: osteoblast and osteoclast. Osteoblasts are cells derived from mesenchymal transformation, whereas osteoclasts are derived from monocytes migrating from the circulation into the bone. Osteoclast precursor cells have receptor activators of nuclear factor-κ B (RANK), whereas osteoblast secreted its ligand, receptor activator of nuclear factor-κ B ligand (RANKL). The binding between these two, RANK and RANKL, will stimulate osteoclast maturation. Only then could the osteoclast perform its duty of releasing calcium from the bone by bone resorption.[8]

Pathophysiology of hypercalcemia in malignancy

In general, hypercalcemia is caused by bone formation and degradation disturbance. In these processes, two cells play a crucial role; osteoblast, which is responsible for bone formation, and osteoclast, which stimulates bone resorption. Under normal conditions, the action of osteoclast is regulated by the binding between the RANK receptor on osteoclast with its ligand, RANKL, on osteoblast, which causes osteoclastogenesis. This binding between RANK and RANKL

Table 1: Clinical manifestations of hypercalcemia in malignancy based on the classification.[22]

Clinical Manifestations	Mild (10.5–11.9)	Moderate (12–14)	Severe (>14)
Cardiovascular	Shortening QT interval, ST segment depression, prolonged PR interval	Shortening QT interval, ST segment depression, prolonged PR interval	Arrhythmia, ventricular tachycardia, ventricular fibrillation, *cardiac arrest*
Gastrointestinal	Constipation, loss of appetite	Nausea, vomit, loss of weight	Acute pancreatitis, peptic ulcer
Renal	Polyuria	Dehydration	Acute kidney injury
Neuropsychiatry	Depression, anxious	Hypo reflex, loss of consciousness	Lethargy, stupor, comma
Musculoskeletal		Weakness	Weakness

could be inhibited by osteoprotegerin secreted by osteoblast, thereby halting the maturation of osteoclast.[2]

In malignancies, hypercalcemia arises through several mechanisms:[2,4]

- Parathyroid hormone-related peptide (PTHrP) secretion causes humoral hypercalcemia.
- Local osteolytic metastasis inducing cytokine release.
- Excessive production of 1,25(OH)2D (calcitriol) by the tumor.
- Primary or ectopic PTH secretion, although this rarely happens.[2,4,10]

Table 1 explains the pathophysiology of hypercalcemia in malignancies and which cancer causes it.[4]

Humoral hypercalcemia

Humoral hypercalcemia occurs in 80% of tumor patients having hypercalcemia. This hypercalcemia usually arises in solid tumors such as squamous cell carcinoma of the head and neck; esophageal, lung, cervix, colon, ovarian, breast, bladder, endometrial cancer; and renal cell carcinoma.[2,4,8] Despite the above, hematological malignancies such as non-Hodgkin lymphoma, the blast phase of chronic granulocytic leukemia, or T-cell lymphoma can also bring about humoral hypercalcemia.[4,8] Humoral hypercalcemia theory, established in 1941 by Fuller Albright, involves PTHrP.[7,10] PTHrP is produced by the parathyroid hormone-like hormone (PTHLH) gene located on the short arm of chromosome 12, while PTH is produced by chromosomes 11.[7,10,14,15]

PTHrP is a gene product commonly expressed by certain tissues such as mesodermal, epithelial, neuroendocrine, and breast tissues. Under normal conditions, PTHrP is steadily secreted and responsible for calcium transport, both transplacental and into the breast milk.[7,8,10,14] PTHrP regulates osteoblast, osteoclast, chondrocyte differentiation, brain development, skin, hair follicle, teeth, hematopoiesis, and vascular smoothness muscle.[7] Nevertheless, PTHrP plays a role in tumor formation in breast cancer.[14]

Structurally, PTHrP is similar to PTH, making PTHrP able to bind to the PTH-1 receptor just like PTH. It activates cyclic adenosine monophosphatase (cAMP), protein kinase A and C, inositol phosphate, and phospholipase C.[4,7,15] In bones, these PTH-1 receptors are located in osteocytes, chondrocytes, and osteoblasts.[15] Bone resorption is then activated, alongside an increase in calcium reabsorption in the distal convoluted tubule and Henle loop of the kidney and an increase in phosphate excretion. In osteoblast, PTHrP increases RANKL synthesis.[2,4,8] Beside that, PTH and PTHrP have other similarities, which are their activities with the calcium-sensing receptor (CaSR). The activity of these receptors located on the surface of the parathyroid gland will be inhibited in hypercalcemia, halting the production of PTH. However, the relationship between PTHrP with CaSR is still a subject under more investigation.[10]

The first 13 amino acids at the aminoterminal end of PTHrP have structural similarities to PTH (Val2, Ser3, Glx4, Gln6, Leu7, His9, Gly12, Lys13), while other parts are distinct from each other.[4,7,15] In this regard, PTHrP does not increase the amount of 1,25(OH)2D (calcitriol), thus not affecting calcium absorption in the intestines. Different than PTH, PTHrP also cannot activate PTH2R.[15] Consequently, humoral hypercalcemia in malignancies contributes to hypercalcemia caused by PTHrP activation on kidneys and bones.[2,4,7,8] In cell T lymphoma, PTHrP production is also triggered by TNF-β activation.[2,4,8] In humoral hypercalcemia, these changes in laboratory parameters could be seen: normal or low calcitriol, intact PTH suppression due to the presence of PTHrP, and an increase in PTHrP. PTHrP can therefore be utilized as a marker to evaluate the response of cancer and antiresorptive treatment.[4]

Local osteolytic metastasis

Hypercalcemia caused by local osteolysis generally accounts for 20% of all hypercalcemia in malignancies. It is usually due to extensive bone metastasis. This condition mainly occurs in tumors such as multiple myeloma, breast cancer with bone metastasis, and leukemia and lymphoma, although

with a much rarer mechanism.[2,4] The primary mechanism of hypercalcemia is indirect bone destruction caused by metastatic cancer cells producing factors that affect osteoclast formation. Generally, these factors are local cytokines such as interleukin (IL)-1, IL-3, IL-6, tumor necrosis factor (TNF)-α, prostaglandin E, lymphotoxin, tumor growth factor (TGF)-α, and TGF-β. These local cytokines caused an increase in RANK/RANKL binding, leading to an increase in the number of osteoclasts and bone resorption.[2,7] Changes in laboratory parameters that could be observed include low to low-normal PTHrP or calcitriol levels, low or intact PTH suppression, and extensive bone infiltration.[4]

In breast cancer, bone metastasis has a very high incidence of 70%.[16] PTHLH and PTHrP play a role in the osteolytic process, mainly locally but also systemically.[4,14,15] An increase of PTHrP leads to an increase in RANKL expression, which binds to RANK and, therefore, promotes fusion, activation, differentiation, and migration of hematopoietic cells involved in osteoclast formation. Excessive bone resorption then commences and will cause hypercalcemia. Besides that, breast cancer cells also increase proinflammatory cytokines such as IL-1, IL-6, IL-8, and vascular endothelial growth factor (VEGF), increasing PTHrP. The risk of hypercalcemia also increases with antiestrogen and aromatase inhibitor usage. The mechanism behind it is probably due to an increase in bone resorption factor when using these drugs.[4]

Besides PTHrP, another essential factor in bone metastasis in patients with breast cancer is CaSR. CaSR is a class C G protein-coupled receptor expressed in the parathyroid gland, bone, kidney, normal breast epithelial cells, and breast tumor cells, including those which metastasize to bones. In normal conditions, CaSR activation by the chief cells of the parathyroid gland is suppressed. This, in turn, causes PTH to be secreted. In breast cancer, however, calcium, which is high in number, will bind to CaSR, thereby increasing the secretion of PTHrP. After that, PTHrP will increase tumor proliferation by acting as an intracrine tumor, causing the tumor cycle to be continued.[16,17] Picture two explains the activation of CaSR and its relationship to PTHrP in inducing hypercalcemia in breast cancer patients with bone metastases.[16]

In multiple myeloma and some types of lymphoma, the cancer cells infiltrating bone marrow will trigger the release of factors activating osteoclast, coinciding with the absence of bone formation by osteoblast. In this condition, osteoblast differentiation from bone marrow stromal cells is inhibited by paracrine factors. The resulting bone resorption causes extensive loss of bone mass.[4] Another cause of the rise in calcium levels in this regard is the increase of paraprotein secretion, which also increases the number of calcium binding to these paraproteins.[8]

Extrarenal production of calcitriol

Increasing extrarenal production of $1,25(OH)_2D$ is observed in 1% of all hypercalcemia in malignancies. This mechanism mainly occurs in Hodgkin and non-Hodgkin lymphoma, ovarian dysgerminoma, and other nonmalignancy conditions such as sarcoidosis, tuberculosis, and other inflammatory conditions.[2,4,8,10] This mechanism is the prime cause of hypercalcemia in Hodgkin lymphoma and is found in one-third of non-Hodgkin lymphoma patients with hypercalcemia. However, Shallis *et al*. reported that hypercalcemia in non-Hodgkin lymphoma is not mediated by increased extrarenal $1,25(OH)_2D$ and PTHrP. Therefore, the precise mechanism behind hypercalcemia in this type of lymphoma has not yet been revealed.[7,18]

The increase of extrarenal $1,25(OH)_2D$ production in lymphoma is independent of PTH and mediated by the presence of malignant macrophages or lymphocytes. It will cause an increase in calcium absorption and bone resorption. The changes reflected on laboratory parameters are normal or low 25(OH)D levels, increasing calcitriol, and low or suppressed PTH. Hypercalcemia caused by an increase of calcitriol showed a good response when treated with glucocorticoids.[4]

Primary or ectopic secretion of PTH

An increase in PTH secretion could be due to primary or ectopic origin. Hypercalcemia in malignancies due to PTH increase accounts for < 1% of all cases. This condition frequently happens on parathyroid adenoma or hyperplasia, causing hyperparathyroidism. Its incidence peaked at age > 45 years, with female preponderance and risk factors of receiving long-term lithium therapy or head and neck radiation. Hyperparathyroid syndrome could also be caused by tumors such as type 1 and type 2 multiple endocrine neoplasias or primitive neuroectodermal tumors.[2,10] Some other malignancies that have been reported to secrete PTH are lung squamous cell carcinoma, thyroid papillary carcinoma, ovarian carcinoma, gastric carcinoma, pancreas tumor, or metastasizing rhabdomyosarcoma. Hypercalcemia due to primary hyperparathyroidism should be suspected in patients with high PTH and low or normal PTHrP.[4]

Clinical manifestations and classification of hypercalcemia

According to serum calcium levels, hypercalcemia is classified into:

- Mild hypercalcemia: serum calcium level < 12 mg/dl, can be asymptomatic or with mild symptoms such as constipation

- Moderate hypercalcemia: serum calcium level 12–14 mg/dl
- Severe hypercalcemia: serum calcium level > 14 mg/dl.[7,19,20]

The clinical manifestation of hypercalcemia is varied, from asymptomatic, mild symptoms like nausea, vomiting, fatigue, abdominal pain, and polyuria to severe symptoms such as decreased consciousness, arrhythmia, volume depletion, and renal function vasoconstriction that can cause acute kidney failure and nephrogenic diabetes insipidus.[1] Clinical manifestation usually occurs when calcium level rises rapidly or is exceedingly high.[8,9] However, hypercalcemia with characteristics such as those is commonly happening in patients with malignancies, thus making cancer patients more prone to more severe symptoms.[8] If categorized according to the organ system involved, hypercalcemia manifestations could be classified into:[6-9,12,20]

Diagnostic approach to hypercalcemia

Hypercalcemia is diagnosed based on a laboratory exam that detects high calcium levels. In blood, calcium is present as blood calcium and calcium ions. These two parameters can be used to diagnose hypercalcemia, although both have their limitations. Blood calcium is an inactive form that binds to albumin, and thereby, its levels are closely dependent on albumin levels.[2,8] For example, in patients with malnutrition with protein-energy wasting, blood calcium can be low as the albumin level is also low. On the other hand, patients with severe dehydration could present with high calcium levels because of high albumin levels.[8] Below are the formula to calculate blood calcium levels based on albumin level in the blood:[2]

$$\textit{Corrected calcium} = 0.8 \times (4 - \textit{serum albumin}) + \textit{serum calcium}$$

Meanwhile, the calcium ion levels in the blood, which is the active form, can be directly interpreted to diagnose hypercalcemia, unlike blood calcium levels that need correction. However, its concentration depends on blood pH. A decrease in blood pH could increase ion calcium levels.[2] Hence, the use of ion calcium is more recommended as the basis for hypercalcemia diagnosis.[8] Laboratory calcium examinations are suggested to be repeated for confirmation before finding the cause of hypercalcemia. Nevertheless, the need for this confirmation does not hinder prompt initial management with fluid expansion.[4,8]

In patients having severe hypercalcemia for the first time, malignancies should be firstly considered as the cause. Therefore, questions such as a history of tumors in the family, exposure to carcinogenic agents, smoking history, drinking history, UV exposure, weight loss, chronic cough, and presence of mass or lump must be included in the history taking. Besides that, a thorough physical examination (including looking for the presence of mass like lymph node enlargement, breast examination, digital rectal examination, or other examinations in other parts of the body) must be performed.[8,12] In investigating the cause of hypercalcemia, laboratory examinations that should be ordered are the levels of phosphate, PTH or PTHrP, 25(OH)D and $1,25(OH)_2D$, calcium, 24-hour urine creatinine, and kidney functions through serum creatinine and glomerulus filtration rate.[2] Table 2 shows the list of laboratory parameters that are recommended to be ordered based on the cause of hypercalcemia on malignancies.[7]

Generally, the first value that could be checked in hypercalcemia patients is intact PTH examination. If the number is high, hyperparathyroidism should be considered for the working diagnosis. If the number is normal or slightly high, a diagnosis of primary hyperparathyroidism or familial hypocalciuric hypercalcemia (FHH) could be considered. Subsequently, a series of examinations can be done, including PTHrP, calcitriol, calcidiol, and protein electrophoresis.[1,4] Patients suspected of having FHH are recommended to undergo CaSR genetic evaluation and family history taking.[1] Urine calcium and 24-hour urine creatinine are also beneficial for patients with suspicion of FHH.[12] Other genes that play a role in FHH include CaSR, AP2S1, and GNA11.[2] Algorithm for evaluating the cause of hypercalcemia is explained in [Figure 1].

Management

Hypercalcemia in malignancies is one of the oncology emergencies.[8,12] The decision to initiate management depends on the severity of clinical manifestations or the degree of hypercalcemia. For example, patients with severe signs such as decreased consciousness or extremely low calcium levels (<14 mg/dl) call for swift and more aggressive

Table 2: Laboratory parameters by etiology of hypercalcemia in malignancy.[7]

Parameter	Humoral hypercalcemia	Local osteolytic metastasis	Increase in calcitriol
Calcium	High	High	High
Phosphate	Low	High	High
PTH	Low	Low	Low
25(OH)D	Low-High	Low-high	Low or normal
$1,25(OH)_2D$	Low or normal	Low or normal	High
PTHrP	High	Low	Low

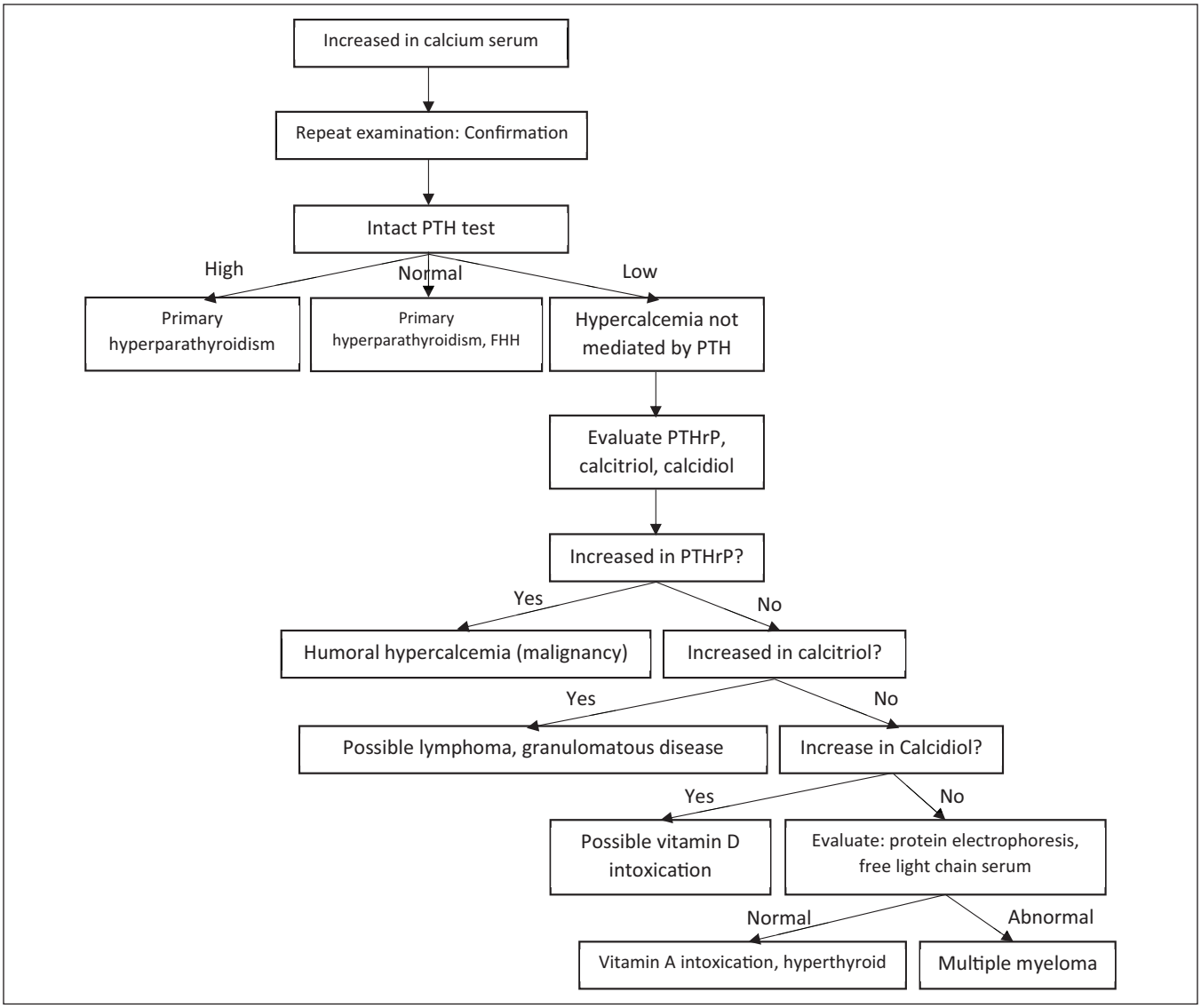

Figure 1: Algorithm for evaluating the cause of hypercalcemia.[4]

management. Below are the approaches for hypercalcemia management based on their degree:[19]

- Mild hypercalcemia. In this early type of hypercalcemia, prompt management is not yet needed. Management is instead focused on avoiding factors that can further increase the patient's blood calcium levels, such as lithium, thiazide diuretics, or a high-calcium diet (>1000 mg/day). Patients are advised to increase fluid intake (6–8 glasses per day) and engage in physical activities. In this condition, another goal is to find the cause of hypercalcemia.[9,19] Prevention for hypophosphatemia should also be done, for instance, with oral supplementation of phosphate.[12]
- Moderate hypercalcemia. Generally, the approach is similar to that of mild hypercalcemia. However, more attentive care should be placed on the possibility of a sudden increase in calcium levels as this needs more aggressive management, just like in severe hypercalcemia.
- Severe hypercalcemia. The most advanced form of hypercalcemia requires an aggressive treatment by administering isotonic saline solution, calcitonin, zoledronic acid, pamidronate, or denosumab. Hydration with saline solution and calcitonin will decrease the calcium levels acutely for around 12–48 hours. Afterward, bisphosphonate administration will provide a long-term lowering effect on calcium levels (2–4 days after).[19]

The management approach to hypercalcemia is made in steps, first targeting the root cause of hypercalcemia, increasing calciuresis, decreasing bone resorption of calcium, lowering intestinal calcium absorption, and finally lowering PTH levels. Furthermore, the management of the malignancies

themselves, which is why hypercalcemia occurs in the first place, is also the goal.[2,9,20,21] This theory is in line with the study conducted by Ramos *et al.* that observed a survival improvement in solid tumor patients with hypercalcemia receiving chemotherapy compared to those not receiving chemotherapy (HR 0,24; 95% CI 0,14–0,4; p < 0,001).[5] Nevertheless, considering that hypercalcemia is a marker that indicates the presence of already advanced or refractory malignancies, a collaborative treatment involving a multidisciplinary palliative team can already be planned after the acute conditions have been remedied.[8,12] A few other strategies that can be done palliatively are debulking surgery to control the symptoms, radiofrequency ablation, liver embolization, cryoablation, or external beam radiotherapy (EBRT).[12,20]

The use of certain drugs that can increase serum calcium levels should also be stopped, for instance, supplementation of calcium or vitamin D, lithium, and thiazide diuretics.[2,20] In an effort to increase calciuresis, intravenous volume expansion has proved to be helpful. On the other hand, decreasing calcium bone resorption could be done by administering bisphosphonate, calcitonin, or denosumab. Glucocorticoids could be given to decrease intestinal calcium absorption, and calcitonin could decrease PTH levels.[2,22] Still, routine monitoring of calcium levels must be carried out to watch the development of hypocalcemia.[22] Table 3 provides a general picture of the strategies of hypercalcemia management.[9,19,20]

Volume expansion

Volume expansion target is to increase urinary calcium excretion and fluid restoration to lower volume depletion triggered by nephrogenic diabetes insipidus and low fluid intake due to nausea and vomiting. Hypovolemia will exacerbate hypercalcemia by disturbing calcium clearance through the kidneys. This expansion volume can be done through intravenous delivery of isotonic saline, firstly with 1–2 liters as a bolus and is continued with 150–300 mL/hour for the next 2–3 days as maintenance. Other literature suggests the initial fluid delivery to be 200–300 mL/hour in patients without edema.[2,20] In this condition, the urine output target is 100–150 mL/hour, necessitating the need for tight monitoring of urine output, central vein pressure (CVP), and fluid balance.[2,19,20] However, a study found that volume expansion did not provide enough reduction of calcium levels when compared to the administration of calcitonin or bisphosphonate, which directly decreases bone resorption.[19]

Additional caution should be exercised, especially in patients prone to fluid overloads, such as those with decreased kidney function, anuria, or heart failure. In such conditions, furosemide can be considered while maintaining electrolyte levels like phosphor and potassium. Strong diuretics, for example, 80–100 mg of furosemide every 1–2 hours, were previously given in patients rehydrated with saline solution reaching 10 liters/day.[2,9,19] Furosemide exerts its effect by inhibiting sodium-potassium-chloride transporter

Table 3: Hypercalcemia treatment.[9,19,20]

Treatment	How to administer	Mechanism	Onset	Duration
Hydration with normal saline	2–4 L/days IV	Intravascular volume expansion, increased urine calcium excretion, increased eGFR	Hour(s)	During administration
Diuretics (not recommended for routine administration)	20–40 mg IV after reaching the rehydration state	Increased urine calcium excretion, which inhibits calcium reabsorption on loop of Henle	Hour(s)	During administration
Calcitonin	4–8 Unit/kg every 6–12 hours SC	Inhibits bone resorption with disturb osteoclast function, increased urine calcium excretion	4–6 hours	48 hours
Bisphosphonate				
Zoledronic acid	3–4 mg IV 15–30 minutes	Inhibits bone resorption with inhibit osteoclast function	24–72 hours	2–4 weeks
Pamidronate	60–90 mg IV 2–6 hours			
Glucocorticoid				
Hydrocortisone	200–400 mg/day IV every 3–5 days continue with prednisone 10–20 mg/day for 7 days or Prednisone 60 mg/day PO for 10 days	Decreased calcium absorption on intestine, decrease in 1,25(OH)2D production on lymphoma patient	2–5 days	Days–weeks
Denosumab	120 mg SC every week for 4 weeks, then every month	Decreased bone resorption with decreased RANKL	4–10 days	4–15 weeks
Calcimimetic	Cinacalcet 60–360 mg PO	Decreased PTH	2–3 days	During administration
Hemodialysis	Calcium dialysate ≤ 1 mmol/l	Low dialysate or without calcium	Hour(s)	During administration

(NKCC2) in the ascending Henle loop, thereby augmenting calcium excretion.[21] Nevertheless, strong diuretics are not recommended for patients not fulfilling the above criteria due to the risk of volume depletion and electrolyte imbalance like hypomagnesemia or hypokalemia.[2,9,12,21]

Calcitonin

Calcitonin is a hormone with amino acid 32, which is intrinsically produced by parafollicular C cells of the thyroid. Calcitonin is reported to have the ability to lower calcium levels up to 2 mg/dl in 72 hours.[9] Calcitonin is beneficial in increasing calcium excretion and abating bone resorption as it hinders osteoclast function. Extrinsically, calcitonin could be obtained from salmon fish as its preparation. Calcitonin is given subcutaneously or intramuscularly with a dose of 4–8 units/kg bodyweight every 6–12 hours. After calcitonin administration, the calcium-lowering effect could happen rapidly, as much as 1–2 mg/dl in the first 4 to 6 hours. However, the tachyphylaxis effect of calcitonin should be observed as it appears mainly in the first 24 to 48 hours. Therefore, calcitonin can only be administered for the first 24–48 hours because afterward, the downregulation of its receptor ensures.[2,19]

Calcitonin provides a satisfactory effect when given together with bisphosphonate. In addition, a simultaneous glucocorticoid administration with calcitonin could enhance the response to calcitonin as it increases the number of receptors in the osteoclast. Calcitonin has side effects, although they rarely happen, such as hypersensitivity and mild nausea.[2] An adjustment for calcitonin dose is not needed in patients with kidney function disorder.[19]

Bisphosphonate

Bisphosphonate is the mainstay of treatment for hypercalcemia in malignancies.[1] Bisphosphonate is a nonhydrolyzed analog of inorganic pyrophosphate, which could absorb the hydroxyapatite surface of the bone and hamper the release of calcium from the bone by inhibiting osteoclast action.[8,19] An induction of osteoclast apoptosis and RANKL stimulation neutralization are how bisphosphonate exerts its bone resorption lowering effect. Bisphosphonate also plays a role in osteoblast differentiation and proliferation and prevents its apoptosis. Besides its ability to lower calcium levels, bisphosphonate can also lower SRE incidence in patients with bone metastasis.[2] In fact, bisphosphonate is more potent in reversing hypercalcemia when compared to fluid expansion and calcitonin administration.[19] Its upper hand is demonstrated in a study by Mousseaux *et al.* that showed bisphosphonate to be the most effective treatment in hypercalcemia. It can lower calcium serum levels until < 12 mg/dl (HR 0,42; 95% CI 0,27–0,67; $p < 0,001$). This study found no significant difference between different types of bisphosphonate such as zoledronic acid, pamidronate, and ibandronate.[6]

Bisphosphonate is recommended to be administered quickly in the first 48 hours of hypercalcemia as its effect will only be seen in 2–4 days after its first administration. Bisphosphonate is also nephrotoxic, making dose adjustments in patients with kidney disorders and tight monitoring of kidney function mandatory.[2] Some bisphosphonate options and doses in hypercalcemia conditions are 4 mg IV zoledronic acid for 15–30 minutes, 60–90 mg of IV pamidronate for 4 hours, or 2–6 mg of IV ibandronate. Zoledronic acid is preferred in lowering calcium levels in malignancies.[19] A repeated dose of bisphosphonate is advised to be given 1 week after the first dose.[8]

There are two generations of bisphosphonate. The first generation, such as clodronate and etidronate, does not contain nitrogen. The second generation, like zoledronic acid, risedronate, alendronate, pamidronate, and ibandronate, contains nitrogen.[8] Ibandronate and etidronate are only available in intravenous form, risedronate and alendronate only in oral form, while clodronate is available both in intravenous and oral form. The administration of oral risedronate and alendronate is not recommended for the acute management of hypercalcemia. Other options that are available in Indonesia are ibandronate and clodronate. In one study, ibandronate was beneficial in treating hypercalcemia in malignancies and could be given at a dose of 2 mg within 1 hour of administration. Clodronate in oral form is more recommended for maintenance to prevent hypercalcemia and SRE in bone metastasis, while its intravenous form is more suitable for acute hypercalcemia.[19]

One side effect that could happen in long-term use (6 months or 2–3 years) of high-dose bisphosphonate is an increased risk of osteonecrosis of the jaw (ONJ) in breast cancer patients with bone metastases or multiple myeloma. However, it rarely happens (1%). The same applies to patients with risk factors such as a history of dental procedures, bad dental and oral hygiene, and smoking. Other rarer adverse effects are uveitis (0.5%), hypophosphatemia, hypocalcemia, femur fractures, and flu-like symptoms.[8,9,19,21]

A decline in kidney function is observed due to acute tubular necrosis caused by zoledronic acid or focal segmental glomerulonecrosis (FSGS) and minimal change disease in pamidronate use.[8,9,19,21] The risk of acute tubular necrosis in zoledronic acid use increases in those with a history of NSAID and bisphosphonate use or advanced-stage cancers.[21] In an attempt to decrease the risk of a further decrease in kidney function among patients with kidney diseases (serum

Table 4: Bisphosphonate dosage adjustment for decreased renal function.[21]

Bisphosphonate according to Crcl	Dosage	Dosage interval
CrCl > 60 mL/minute		
Pamidronate	90 mg during 2–3 hours	Every 3–4 weeks
Zoledronic acid	4 mg during 15 minutes	Every 3–4 weeks
Ibandronate	Not recommended	
CrCl 30–60 mL/minute		
Pamidronate	60–90 mg during 2–3 hours	
Zoledronic acid		Every 3–4 weeks
CrCl 50–60 mL/minute	3.5 mg	Every 3–4 weeks
CrCl 40–49 mL/minute	3.3 mg	
CrCl 30–39 mL/minute	3 mg	
Ibandronate	Not recommended	
CrCl < 30 mL/minute		
Pamidronate	60–90 mg during 4–6 hours	Every 3–4 weeks
Zoledronic acid	Not recommended	
Ibandronate	Not recommended	

creatinine > 4.5 mg/dl for zoledronic acid and creatinine clearance < 30 mL/minutes for pamidronate or ibandronate) requiring bisphosphonate, longer duration or a lower dose could be given (4 mg zoledronic acid in 30–60 minutes, 30–45 mg pamidronate in 4 hours, and 2 mg ibandronate in 1 hour).[8,9,19] Other studies have not yet recommended the use of ibandronate in those with declining kidney function as there are still not enough studies supporting that. Albuminuria examinations like urinary albumin excretion rate (UAER) every 3–6 months are recommended for the above population. The treatment should be terminated if albuminuria happens. Table 4 shows the dose adjustment for bisphosphonates in patients with declining kidney function.[21]

Denosumab

Denosumab is a monoclonal against RANKL, so its administration could decrease the activation, maturation, and function of osteoclast, leading to a diminished bone resorption. Denosumab could be given in hypercalcemia patients who are refractory to bisphosphonate or with contraindications such as a severe decline in kidney function. Denosumab administration is given in 7–30 days, usually in a subcutaneous dose of 120 mg on day-1, -8, -15, -29, and 4 weeks afterward (an initial dose of 60 mg could be given subcutaneously). The effect of denosumab is observed 2–4 days after the first administration. The denosumab effect is more potent in patients with a decline in kidney function, making the need for dose adjustment according to the glomerular filtration rate. Initially, a dose of 0.3 mg/kg bodyweight is given to decrease the hypocalcemic effect. Adverse effects include osteonecrosis of the lower jaw and a much rare atypical fracture.[2,19] More frequent side effects include dyspnea, diarrhea, nausea, or bone tenderness.[8]

Glucocorticoids

Glucocorticoids are given in hypercalcemia caused by increased extrarenal $1,25(OH)_2D$ (commonly occurs in lymphoma or ovarian dysgerminoma) or in multiple myeloma patients. Glucocorticoids can hamper bone resorption by osteoclast by lowering the cytokines produced by tumors, specifically 1α-hydroxylase that converts 25(OH) D (calcidiol) into $1,25(OH)_2D$ (calcitriol). Another expected effect of glucocorticoids is to obstruct calcium absorption from the intestines.[2,9]

Glucocorticoids are usually given to patients with granulomatous diseases, such as sarcoidosis or lymphoma, in which calcitriol increases. The recommended regimen is 200–400 mg/day of hydrocortisone for 3–4 days, continued with 10–20 mg/day of prednisone for 7 days, or 40–60 mg/day of prednisone for 10 days. Glucocorticoids are reported to lower serum calcium by > 3 mg/dl after 1 week of treatment.[2,9] Side effects that need to be observed are hypertension, hyperglycemia, peptic ulcer disease, psychiatric disorder, and muscle weakness.[8]

Hemodialysis

Hemodialysis is the treatment of choice in severe hypercalcemia presenting with symptoms such as a decrease in consciousness. This usually happens when calcium level is severely low, reaching 18–20 mg/dl, in heart failure or oliguric end-stage renal disease patients who did not receive adequate hydration.[6,22] Hemodialysis can also be done in severe hypercalcemia unresponsive to conservative treatments like hydration and bisphosphonate.[9] Hemodialysis could be performed with low or no-calcium dialysate solution (dialysate calcium levels of ≤ 1 mmol/l).[1,19,21] Hemodialysis could decrease calcium levels by 3–5 mg/dl in 3–4 hours.[9]

Calcimimetic

Calcimimetics, such as cinacalcet, lowers high serum calcium levels usually experienced in patients with secondary hyperparathyroidism undergoing hemodialysis or parathyroid malignancies. It acts through the CaSR allosteric modulator mechanism in parathyroid cells, leading to a decrease in PTH productions and effects.[9,16,19] Because of that, cinacalcet is believed to be beneficial in the management of hypercalcemia in malignancies where PTH

production increases ectopically.[10] Meanwhile, its effect on hypercalcemia in malignancies with osteolytic metastases is unknown.[16] CaSR is also present in kidney and bone tissues, involved in osteoblast differentiation and bone resorption by osteoclast.[9] Cinacalcet is usually given with a starting dose of 60–360 mg/day orally, with possible side effects like headache, nausea, and vomiting.[8]

Other managements

Another treatment for hypercalcemia in malignancies, which is currently still under research, is the antibody against PTHrP. Studies on this PTHrP antibody are still limited to animals (in this case, rats) and are reported to have calcium-lowering effects while suppressing cytokines produced by cancer cells.[9,22] Administration of intermittent PTH (teriparatide) or PTHrP analog (abaloparatide) has also been thought to reduce the effect of hypercalcemia caused by osteolytic metastasis. However, their use is not yet recommended due to their narrow safety profile.[16]

Previously, intravenous gallium nitric administration with a dose of 200 mg/m^2 for 5 days could lower calcium levels by inhibiting osteoclast activity and increasing calcium secretion into the urine. Nevertheless, gallium nitric has been withdrawn from the market as it has severe adverse effects such as anemia, hypophosphatemia, and acute tubular necrosis.[7,8,20-22] Another proposed medication is mithramycin, a cytotoxic antibiotic that can lower calcium by inhibiting bone resorption by osteoclast. This drug is given intravenously with a 25 mcg/kg bodyweight dose for 4–6 hours. It will exert its effect within 12 hours and can be repeated once every 3–4 days. Nonetheless, mithramycin is not recommended due to its side effects such as thrombocytopenia, stomatitis, nausea, vomiting, hepatotoxicity, and nephrotoxicity.[20]

CONCLUSION

Hypercalcemia is one of the most common complications found in malignancies, with prevalence reaching 30%. It is a prognostic marker for malignancies which indicates that the cancer is recurrent or already in an advanced stage. There are four main mechanisms through which hypercalcemia occurs in malignancies: humoral hypercalcemia mediated by PTHrP (80%), local osteolytic metastasis (20%), an increase of extrarenal calcitriol production (1%), and primary or ectopic PTH production (<1%). According to its severity, hypercalcemia is divided into mild (serum calcium levels < 12 mg/dl), moderate (12–14 mg/dl), and severe (>14 mg/dl). Hypercalcemia caused by tumors is generally severe and develops rapidly. The clinical manifestations could affect various systems, for instance, musculoskeletal, gastrointestinal, genitourinary, cardiovascular, and neuropsychiatry.

In general, the management of hypercalcemia is targeted toward the moderate and severe forms. It begins with intravenous saline solution administration as a volume expander, followed by calcitonin and bisphosphonate. Other additional treatments are adjusted according to specific indications. For example, denosumab for hypercalcemia is unresponsive to bisphosphonates and glucocorticoids when there is an increase in calcitriol, calcimimetic as an allosteric modulator of CaSR, and hemodialysis in severe hypercalcemia in which volume expansion is contraindicated. Further studies are needed to understand better various novel treatments for hypercalcemia, like PTHrP antibodies, PTH analog, or PTHrP analog.

Declaration of patients consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

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