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DIVISION OF RADIATION ONCOLOGY

INCIDENCE AND TREATMENT OF HYPERCALCEMIA IN CANCER PATIENTS RECEIVING RADIOTHERAPY –A RETROSPECTIVE REVIEW OF PRACTICE AT CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL (CMJAH) FROM 2012 TO 2015

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A research report submitted to the Faculty of Medicine in a partial fulfillment of the requirements for a degree of Master of Medicine in the specialty of Radiation Oncology (MMED Rad Onc) at the University of the Witwatersrand, Johannesburg

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DECLARATION

I, JERRY NDUMBALO, declare that this research report is my own original work. It is being submitted for the degree of Master of Medicine in the specialty of Radiation Oncology in the University of the Witwatersrand, Johannesburg.

This thesis has been submitted for fellowship for Colleges of Medicines in Radiation Oncology South Africa in 2016 as a requirement for final FC Rad Onc Part II examination.

The 27th of October 2017 Place: Johannesburg

DEDICATION

To my parents, Mr Rogers Ndumbalo (RIP) and Mrs M. Ndumbalo for their Love and encouragement, my wife Domina for her love and support, my children Rogers and Alvin for their patience, my grandmother Monica Nchai and Leocadia Bahegwa my mother in-law for their prayers, my teachers for their untiring mentorship and to my patients for allowing me to take care of them, treat them and learn from them.

ABSTRACT

Background: Cancer induced hypercalcemia (CIH) is the most frequent metabolic oncologic emergency and occurs in up to 44.1% of all cancer patients at some time in their disease course. It occurs in patients with both solid and hematologic malignancies. CIH occurs mostly in patients with advanced cancer and is an indicator of poor prognosis. Timely diagnosis and intervention is lifesaving and also may enhance patient compliance with primary and supportive treatment and quality of life. This study aimed to describe the incidence, clinical patterns and treatment outcomes of hypercalcemia in cancer patients receiving Radiation therapy in Charlotte Maxeke Johannesburg Academic Hospital, Johannesburg.

Materials and Methods: This was a retrospective descriptive study, 125 patients who were admitted at the Radiation oncology ward CMJAH for hypercalcemia management from January 2012 to December 2015, were analyzed. Demographic data, relevant clinical information such as Stage of the disease, type of cancer, level of hypercalcemia, toxicity and Response to the treatment were recorded. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS_version 23). The incidence of hypercalcemia, clinical patterns, treatment outcomes and toxicities were evaluated. The study was approved by the Human Research Ethics Committee medical (HRECM) of the University of Witwatersrand with Clearance certificate number M140546.

Results: Of the 125 patients analysed, males to females ratio was 1:1. The most frequent site of primary cancer diagnosis in patients with hypercalcemia was gynaecological malignancies 31 (24.8%), followed by head and neck cancers 23 (18.4%), prostate 19 (15.2%), breast cancer 17 (13.6%), gastrointestinal malignancies 12 (9.6%), multiple myeloma 5 (4%), lung cancer 3 (2.4%) and other malignancies 15 (12%). Most patients had metastatic disease and uncontrolled primary disease 78 (62.4%) compared to primary controlled disease 47 (37.6%). Bone metastasis were present in 51 (41%) of patients.

Clinical presentation of patients with hypercalcemia was mainly Neuromuscular 41 (32.8%), nausea/vomiting 37 (29.6%), Polyuria 20 (16%), mental 16 (12.8) and Polydipsia 9 (7.2%).

Most of patients had severe hypercalcemia with pre-treatment corrected serum calcium level of > 2.9 mmol/L 77 (61.6%), 28 (22.4%) had Corrected serum Calcium between 2.71-2.89 mmol/L and 20 (16%) had corrected serum calcium between 2.56-2.70 mmol/L. One hundred and four patients (83.2%) received hydration + bisphosphonates and 21 (16.8%) of patients received hydration alone and non-received haemodialysis.

One week post treatment majority of patients had ≤2.55 mmol/L Serum level of Calcium 81 (64.8%), 11 patients (8.8%) had serum level of calcium 2.56-2.71 mmol/L, 23 patients (18.4%) had serum calcium between 2.71-2.89 mmol/L and only 10 patients (8.0%) had serum level of calcium ≥2.9 mmol/L. The corrected serum calcium was 2.4770 ± 0.34512 mmol/L one week after treatment.

One month post treatment majority of patients 99 (79.2%) remains to have normal serum level of calcium ≤2.55 mmol/L and only about 11 (8.8%) patients had ≥2.9 mmol/L.

Forty four patients (35.2%) had relapse in 33 days (median) time and were subsequently treated with hydration and bisphosphonates. As the patients were enrolled from radiation oncology ward, most were treated with either radiation alone 72 (57.6%) or Concurrent chemo radiation 15 (12.0%) as treatment modalities for their primary cancer. Patients who received chemotherapy first and then radiotherapy for the treatment for their primary cancer were 37 (29.6%).

Fourteen (58%) patients with pre-treatment calcium level of 2.56-2.70 mmol/L received hydration alone and 76 (98%) of patients with serum pre-treatment calcium of ≥2.9 mmol/L were treated with hydration + bisphosphonates (P=0.001). Side effects to bisphosphonates were mainly gastrointestinal: Nausea/vomiting 42 (33.6%) patients, Constipation 14 (11.2%), abdominal pain 13 (10.4), Diarrhoea 11 (8.8) and anorexia 1 (0.8) patients. Other toxicities reported were fever 12 (9.6%) patients and hypocalcaemia 14 (11.2%). Eighteen patients (14.4%) did not report any side effect to treatment.

Conclusion: Hypercalcemia of malignancy is a common finding in patients with advanced stage cancers. Hypercalcemia of malignancy usually presents with markedly elevated calcium levels and patients are therefore usually symptomatic. For acute management of hypercalcemia, rehydration is the mainstay of treatment because all patients tend to have

dehydration. Bisphosphonates are potent calcium lowering agents, but they require careful administration and are contraindicated in patients with declined renal function. Common bisphosphonates toxicities are mainly gastrointestinal: Nausea/vomiting, constipation, abdominal pain, diarrhoea and anorexia. Other toxicities reported were fever and hypocalcaemia.

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ABBREVIATIONS

BP	Bisphosphonates
Ca2+	Calcium
CIH	Cancer induced hypercalcemia
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
ECG	Electrocardiogram
EGF	Epidermal growth factor
FBC	Full blood count
GIT	Gastrointestinal tumours
Hb	Haemoglobin
HRECM	Human Research Ethics Committee medical
IGF 1	Insulin-like growth factor 1
M	Median
MAPK	Mitogen-activated protein kinase
OAF	Osteoclast activating factor
OIF	Osteoclast inhibitory factor
OPG	Osteoprotegerin
PGs	Prostaglandins
PTH	Parathyroid Hormone
PTHrP	Parathyroid hormone-related protein
RANK	Receptor activator of nuclear factor k B
RANKL	Receptor activator of nuclear factor k B ligand

SD	Standard deviation
SQ	Subcutaneous
SRE	Skeletal related events
TGF	Tumour growth factor
TNF	Tumor necrosis factor
U/E	Urea and electrolyte
Yrs	Years

CHAPTER ONE

1.0. Introduction and background

Hypercalcemia is defined as an increased serum calcium level above the normal upper limit for a given reference value used in a laboratory (1, 4). Cancer induced hypercalcemia (CIH) and primary hyperparathyroidism are the most and second most common causes of hypercalcemia in hospital in-patients, respectively (1, 5, 6).

Cancer induced hypercalcemia (CIH) is the most frequent metabolic oncologic emergency and occurs in up to 44.1% of all cancer patients at some time in their disease course (2, 4, 7). It occurs in patients with both solid and hematologic malignancies. Types of cancer commonly associated with CIH include Squamous cell carcinoma of the lung, head and neck, and esophagus; multiple myeloma; renal cell carcinoma; ovarian carcinoma and lymphoma. Lung cancer, breast cancer and multiple myeloma have the highest incidence of CIH, accounting for more than 50%, while the condition occurs rarely in patients with colorectal carcinoma (8, 9). More than 30% of patients with multiple myeloma, 25% of those with squamous cell carcinoma and 20% of those with breast cancer may develop CIH (10). Tumors rarely associated with CIH include central nervous system malignancies and prostate cancer, as well as stomach and colorectal adenocarcinoma (8).

Cancer induced hypercalcemia (CIH) is particularly common in patients with advanced cancer (20-40%) and is an indicator of poor prognosis with a mean survival rate of 2-3 months (3, 11). The extent of metastatic bone disease correlates poorly with both the occurrence and severity of CIH (46). Patients with CIH tend to have limited survival of several months (12).

Timely diagnosis and intervention is lifesaving and also may enhance patient compliance with primary and supportive treatment and quality of life (2).

1.1. Normal Regulation of Calcium Metabolism

Calcium is important in biochemical reactions such as muscle contraction, bone development and coagulation among others (13). Approximately 10-20% of ingested calcium is absorbed in the small intestine (13). Calcium is present in two major compartments: Bone (major part of body calcium) and plasma (13). In plasma, serum calcium is present in several forms, such as free or ionized calcium, which is actually a physiologically active form corresponding to approximately 45% of serum calcium, with 65% of calcium being bound to various carriers, such as albumin (40% of calcium), citric acid, sulfate, and phosphate (13).

Calcium absorption and metabolism is regulated by several hormonal mechanisms. When calcium levels drop below 2.5 mmol/L, this activates calcium-sensing cells in the parathyroid glands to stimulate the release of Parathyroid Hormone (PTH) (13).

When PTH is released, it activates the 1-alpha-hydroxylase enzyme located in the renal proximal tubules, which converts 25-hydroxyvitamin D into active form 1,25-dihydroxyvitamin D (7). PTH also stimulates calcium reabsorption in the distal part of the nephron and renal phosphorus excretion. Calcium is then mobilized from the bone with the help of 1,25-dihydroxyvitamin D. All these leads to an increase in serum calcium concentrations and bringing them back to normal (13).

Vitamin D is another key player in normal calcium metabolism. When converted to its active form 1,25-dihydroxycholecalciferol in the liver and kidneys, it increases the absorption of calcium and phosphate in the gastrointestinal tract, decreases the renal excretion of calcium and phosphate, and with the participation of PTH leads to increased calcium release from the bone and subsequent bone de-mineralization (13).

Calcitonin, a thyroid hormone produced by thyroid C cells is also important in calcium normal physiology. When calcium concentration increases the calcitonin release is augmented which limits bone remodeling and calcium release from the bone and also calcium reabsorption in the kidneys (14).

In conclusion, interaction between calcium levels, PTH, Vitamin D, and bone cells regulates bone metabolism and calcium release from the bones.

1.2. Etiology and pathophysiology of Cancer induced hypercalcemia.

Three major mechanisms by which CIH can be mediated are; tumor secretion of parathyroid hormone-related protein (PTHrP) also known as Humoral hypercalcemia of malignancy (80%); osteolytic metastases (20%) with local release of cytokines (including osteoclast activating factors); and tumor production of 1,25-dihydroxyvitamin D (calcitriol) (1,3) (Table1).

Table 1: Mechanisms of Hypercalcemia of Malignancy

Mechanism	Malignancies	Frequencies (%)
PTHrP production	Squamous cell carcinomas: lung, cervical, esophageal, oral and laryngeal cancers Certain lymphomas: non-Hodgkin's, T-cell lymphoma Adenocarcinomas: breast and ovary Renal cell carcinoma Transitional cell carcinoma Multiple myeloma (rare)	80
Local Osteolysis	Multiple myeloma (frequent) Solid malignancies: breast, prostate and lung cancers. Lymphomas	20
Secretion of 1,25-dihydroxyvitamin D (calcitriol)	Multiple myeloma Lymphomas: Hodgkin's, non-Hodgkin's	

The cellular basis for the former two mechanisms includes changes in the activity and balance at the level of the bone-remodeling unit. Bone turnover involves the highly coordinated activity of two distinct types of cells, the osteoblast, or bone-forming cell and the osteoclast, or bone-removing cell (3, 15). Communication between osteoblasts and osteoclasts primarily involves the receptor activator of nuclear factor k B (RANK) ligand (RANKL) signaling pathway (3, 15).

RANK is a receptor expressed on osteoclast precursor cells. The naturally occurring ligand, RANKL, is produced by osteoblasts and drives proliferation and differentiation of the osteoclasts into mature, multinucleated units. In addition, the osteoblast cell produces osteoprotegerin (OPG), a decoy receptor that binds to and inactivates RANKL (3, 15).

Osteoblast is the focal point for the integration of endocrine and paracrine signals that alter bone remodeling. Osteoblast cells express estrogen receptors that when occupied with ligand can reduce RANKL and increase OPG (3, 15). Osteoblasts also express the cell surface receptor for parathyroid hormone (PTH) and parathyroid hormone–related hormone (PTHrP), PTH1R (3, 15). Both PTH and PTHrP stimulate PTH1R, which, in turn, increases osteoblast activity and RANKL signalling to the osteoclast. In sum, PTH/PTHrP signaling results in an increased bone turnover with a greater increase in bone resorption than formation, resulting in a net efflux of calcium and hypercalcemia from the bone microenvironment (see Figure 1).

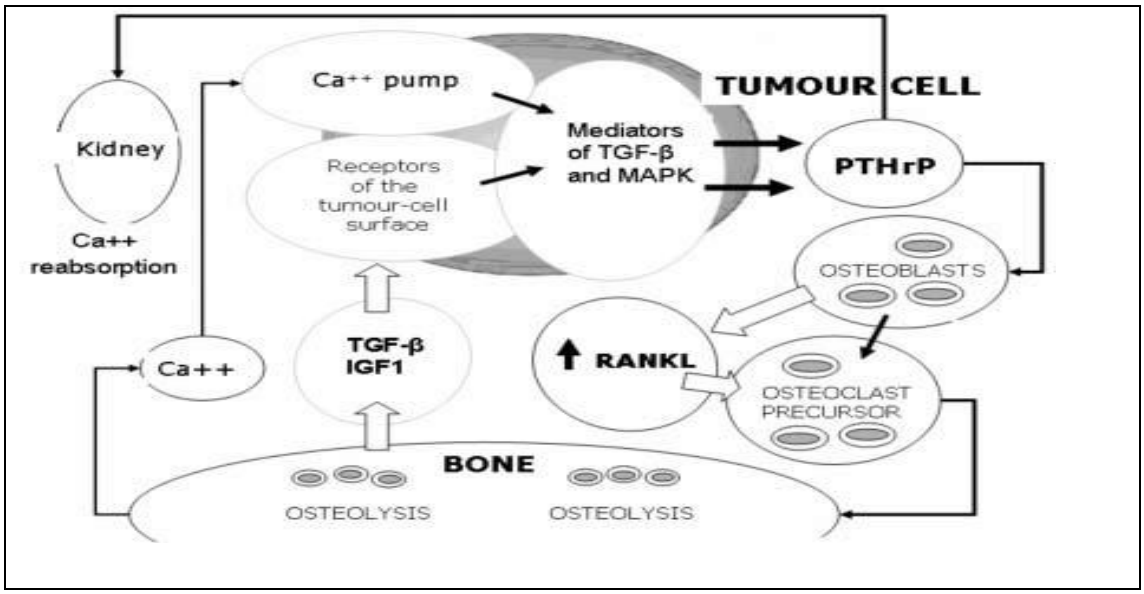

Figure 1: Interactions between osteoclasts and cancer cells

Tumors that commonly produce PTHrP include squamous cell carcinomas of the lung, cervix, and esophagus; certain lymphomas; renal cell carcinoma; and adenocarcinoma of the breast, prostate, and ovary (16).

The second mechanism by which malignancies cause hypercalcemia includes osteolytic metastases and excessive calcium release from bone, accounting for approximately 20% of malignancy-related hypercalcemia (3). Local osteolysis as the basis for hypercalcemia occurs most frequently in widely metastatic disease (eg; breast and lung cancers), and the degree of hypercalcemia correlates with the extent of tumor burden (3).

Multiple myeloma also present with significant areas of osteolysis and hypercalcemia (17). Underlying the release of calcium from the bone microenvironment is increased osteoclast activity, probably due to PTHrP and other factors that can increase resorption (17).

The third mechanism includes ectopic activity of 1-alpha-hydroxylase and the formation of 1,25-dihydroxycholecalciferol. Vitamin D enhances calcium and phosphate absorption from the intestinal tract. Stored vitamin D (25-[OH]D) is 1-hydroxylated in the kidney to the active compound 1,25- (OH)2D. PTH actively drives the 1-hydroxylase step at the kidney (18). Patients with Hodgkin lymphoma, non-Hodgkin lymphoma, as well as multiple myeloma, have been described as having vitamin D–mediated hypercalcemia (18). In these patients, 1,25-(OH)2D levels, along with calcium levels, are high while PTH is suppressed from the negative feedback to the parathyroid cells. Similarly, measurements of bone turnover markers are low in vitamin D–mediated hypercalcemia because the reduction in PTH results in a diminution of osteoblast and osteoclast activity (18).

1.3. Diagnosis

Hypercalcemia may be classified based on total serum and ionized calcium levels, as follows: Normal serum calcium levels are 2.0 to 2.55 mmol/L (see Figure 2). Hypercalcemia is considered mild if the total serum calcium level is between 2.56 and 3 mmol/L. Levels higher than 3.5 mmol/L can be life threatening (19).

Hypercalcemia was defined as serum calcium higher than 2.55 mmol/L which is the upper normal limit of serum calcium measurement for the central laboratory at CMJAH-Johannesburg, after correction with serum albumin using the following formula:

Corrected serum calcium = measured serum calcium + [(4-serum albumin) x 0.8].

After treatment, patients who had corrected serum calcium of less than 2.55 mmol/L were defined as responders.

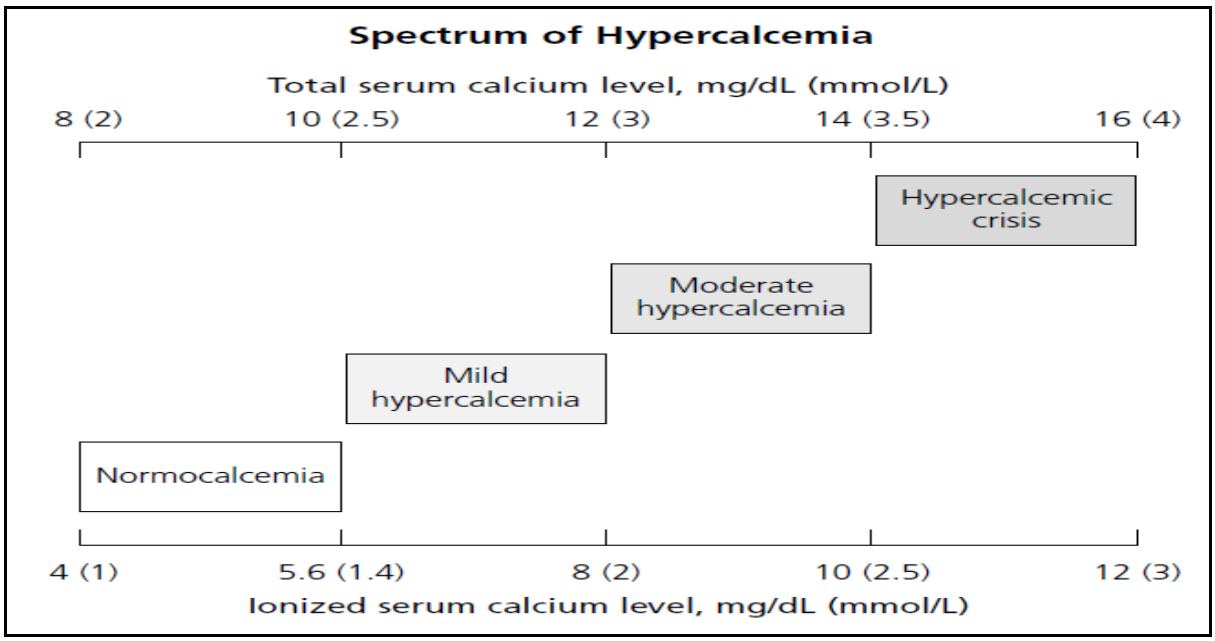

Figure 2: Spectrum of hypercalcemia indicated by serum total and ionized calcium levels.

1.4. Clinical presentation of Hypercalcemia of Malignancy.

The clinical manifestations of hypercalcemia are generally constitutional in nature, non-specific, and independent of etiology (20).

The degree of CIH, along with the rate of rise of serum calcium concentration, often determines symptoms and the urgency of therapy (1, 2). Patients with mild hypercalcemia (Ca^{2+} < 3 mmol/L) may be asymptomatic, or they may report vague or nonspecific symptoms, such as constipation, fatigue, and depression. A serum calcium of (3 to 3.5 mmol/L) may be well-tolerated chronically, while an acute rise to these concentrations may cause marked symptoms, including polyuria, polydipsia, dehydration, anorexia, nausea, muscle weakness, and changes in sensorium. In patients with severe hypercalcemia (calcium >3.5 mmol/L), there is often progression of these symptoms (2) (Table 2).

Neurocognitive symptoms may include some behavioral disturbances, such as anxiety, mood changes and a decrease in cognitive function. In cancer patients with higher values of calcium, they may develop more severe presentations, such as changes in mental status, including coma (21).

Renal manifestations of hypercalcemia consist of nephrogenic diabetes insipidus with resultant polyuria, renal vasoconstriction, distal renal tubular acidosis, and in more chronic cases, nephrolithiasis, tubular dysfunction, and chronic renal failure (22, 23).

Hypercalcemia also affects the gastrointestinal system. Mild hypercalcemia may present as anorexia and constipation (24). Patients with more advanced hypercalcemia may develop nausea and vomiting.

Cardiovascular system may also be affected by elevated calcium. Patients with hypercalcemia typically have a shortened QT interval on the electrocardiogram (ECG) (25). Severe hypercalcemia may mimic ST-segment elevation myocardial infarction on the ECG (25). Patients with severe hypercalcemia may develop malignant ventricular arrhythmias such as ventricular fibrillation (26).

Table 2: Clinical Manifestations of Hypercalcemia of Malignancy

Symptoms	**Signs**
General	
Fatigue, lethargy, pruritis	Dehydration
Cardiac	
Palpitations	Atrial arrhythmias, ventricular arrhythmias, shortened QT interval, prolonged PR interval, Bradycardia
Neurologic	
Muscle weakness, confusion	Hyporeflexia, obtundation, pyschosis, seizure, coma
Gastrointestinal	
Nausea, vomiting, constipation	Internal ileus, distension
Renal	
Polyuria	Renal failure
Skeletal	
Bone pain	Bone fracture

1.5. Management of Cancer induced hypercalcemia

The management of CIH is based on the presence of symptomatology and the severity of calcium elevation. Patients with asymptomatic or mildly symptomatic (eg, constipation) hypercalcemia (Below calcium 3 mmol/L) do not require immediate treatment. Similarly, a serum calcium of 3 to 3.5 mmol/L may be well-tolerated chronically, and may not require immediate treatment. However, an acute rise to these concentrations may cause marked changes in sensorium, which requires more aggressive measures. In addition, patients with a serum calcium concentration 3.5mmol/L require treatment, regardless of symptoms (44).

Management of CIH includes hydration, calcitonin, bisphosphonates, denosumab, and in certain patients, prednisone and cinacalcet. Hemodialysis should be considered in patients with advanced underlying kidney disease and refractory severe hypercalcemia (37, 38, 39).

The first step of management of CIH should be to assess the hydration status and saline infusion is currently the standard of treatment, depending upon the severity of dehydration. Hydration alone may be sufficient for asymptomatic patients with borderline serum calcium (37). Adequate hydration reduces serum calcium by a medium of 0.25 mmol/L (38).

Start patients with advanced hypercalcemia at a rate of around 200-300 ml/h and reassess them periodically for signs of fluid overload (shortness of breath, edema, etc.). Re-hydration with 2 to 3 litres per day is now the accepted practice with daily serum electrolyte measurement to prevent hypokalemia and hyponatremia for cases of severe or symptomatic hypercalcemia (37, 39). Increase patient's oral fluid intake to 2 to 3 litres per day, as tolerated (37).

The rate of IV hydration should be decreased in patients with underlying cardiac and renal disease to minimize the risk of symptomatic fluid overload. Loop diuretics (i.e. furosemide, 20 to 40 mg IV, every 2 hours) enhance calcium excretion only after normovolemia has been reached but the routine use is not recommended due to the development of volume depletion and electrolyte abnormalities. Thiazide diuretics should be avoided, as they worsen hypercalcemia (27).

Bisphosphonates (BP) represent at present the drugs of choice for treating patients with CIH. They work by inhibiting osteoclasts, inducing apoptosis in these cells and bind to bone,

blocking osteoclastic resorption and osteolysis. Once inside osteoclasts, BPs hamper adhesion to the mineralized matrix, reduce lysosomal enzymes and activate a pro-apoptotic pathway (3).

Bisphosphonates are appropriate to administer when serum calcium (corrected) is greater than or equal to 3 mmol/L or when serum calcium (corrected) is less than 3 mmol/L when accompanied by symptoms (38).

Bisphosphonates (BPs) effectively lower the serum calcium level with maximum effect seen in 2 to 4 days. The duration of effect is usually several weeks and varies among patients and with the type of BP. Patients treated with BP have a delayed time to skeletal fracture, and a reduced need for radiation therapy and orthopedic surgery to treat bone metastases (3).

Bisphosphonates (BPs) are subdivided into two groups: First and second-generation BPs. The first-generation or non-nitrogen-containing bisphosphonates include etidronate and clodronate, which are less commonly used nowadays. The second generation or nitrogen-containing bisphosphonates include such medications as alendronate, risedronate, ibandronate, pamidronate, and zoledronic acid, which are generally more potent than the first-generation bisphosphonates (27, 28).

Pamidronate is able to normalize calcium levels in 80% to 100% of patients and the infusion time of 2-4 hours does not show a significant increment of nephrotoxicity (1, 27). Randomized trials have proved that pamidronate is superior to clodronate, etidronate and mithramycin (1, 27).

Zoledronate is a second-generation BP and can be administered in a dose 10 times lower than pamidronate (1, 27). It has been shown to be superior to pamidronate in the rate of normocalcemia, duration of control of CIH and time to relapse (1 to 1.5 months) (50). The rate of normalizing serum calcium is significantly higher for zoledronic-acid-treated patients (88.4% for 4 mg and 86.7% for 8 mg) than for pamidronate disodium-treated patients (69.7%) (50). It is given in a 15-minute IV infusion (4 mg), and it is approved for use only in the CIH, while higher doses can be used in relapsing or refractory patients (1, 27).

Its use is contraindicated if creatinine clearance is below 30 ml/min and/or if other nephrotoxic drugs are administered to the patient (1, 27). Fever is a common side effect of zoledronic acid, with renal impairment seen rarely (40).

Pamidronate is given by IV infusion over 4 to 24 hours. The initial dose varies: 30 mg if the Ca2+ < 3 mmol/L, 60 mg if the Ca2+ is 3-3.5 mmol/L and 90 mg if the calcium level is even higher level. A subsequent dose should not be given until after 7 days. Because of the lag in onset of effect, BPs should be combined with faster acting therapeutic modalities, such as IV saline infusion and calcitonin injections. Pamidronate is effective in normalizing serum calcium levels in 80%-94% of patients (49).

Ibandronate is another BP useful in patients with breast or hematological cancer (29). A randomized trial comparing ibandronate and pamidronate showed a comparable activity of the two drugs in reducing calcium levels, while the median duration of response appeared to be longer for ibandronate (30). Ibandronate significantly lowered serum calcium levels in up to 77% of patients after 5 days (47, 48). The dose of ibandronate is 150 mg orally once monthly. The tablet should be taken on the same day of each month. It has an extremely low rate of nephrotoxicity and no dose reductions are needed for patients with moderate renal impairment or those treated with concomitant nephrotoxic therapies (29).

Bisphosphonates side effects include flu-like symptoms, ocular symptoms, acute kidney injury, new-onset nephrotic syndrome, esophageal inflammation (typically for orally administered drugs), and very rarely osteonecrosis of the jaw (28). Osteonecrosis of the jaw is mostly reported in patients with multiple myeloma or metastatic bone disease receiving high potency bisphosphonates, such as zoledronic acid and denosumab, which is a monoclonal antibody to RANKL (32).

Denosumab is the human monoclonal antibody able to interfere with RANKL-RANK pathways (31). This agent showed a rapid and sustained dose-dependent decrease of bone turnover, when administered to postmenopausal osteoporotic women. Denosumab is superior to zoledronic acid in preventing skeletal related events (SRE) with favorable safety and convenience in patients with bone metastases from advanced cancer (31).

Denosumab has been shown to be effective in hypercalcemia refractory to bisphosphonates (33). The dose is 120 mg subcutaneously, and it should be repeated no earlier than 7 days following the first administration (34). Its effects are seen within 2-4 days after the administration.

Common side effects of denosumab include bone pain, nausea, diarrhea, shortness of breath, and in rare instances osteonecrosis of the jaw, which is usually seen in patients treated with denosumab for at least several months (5, 35).

There were many other treatments used in CIH before the advent of BPs, including corticosteroids, calcitonin, plicamycin, and gallium nitrate (3).

Steroids are particularly useful for hypercalcemia seen with lymphomas and multiple myeloma (40). Corticosteroids may lower serum calcium if they have an antineoplastic effect on the underlying malignancy (38). They should be reserved for situations in which bisphosphonates are not easily accessible or are ineffective or in which other indication for corticosteroids (pain or nausea) exist (38). Doses of steroids commonly used are prednisone 40 to 100 mg daily for up to one week (37); hydrocortisone 100 mg I.V. q6h (42); and dexamethasone 4 mg S.C. q6h for 3 to 5 days (42).

Calcitonin is rarely used, despite the fact that it works rapidly, because its effect is short lived (2 to 3 days); repeated doses of calcitonin are less effective because patients develop tolerance to the calcium-lowering effect due to the down regulation of calcitonin receptors in osteoclasts. Calcitonin can be used initially with BPs in cases of severe symptoms and very high calcium levels to incur a rapid response and allow time for the BPs to work. The usual dose of calcitonin is 100units subcutaneously 3 times a day for 1 to 2 days (3). Possible side effects: flushing, mild nausea, crampy abdominal pain. A small risk of hypersensitivity exists due to salmon derivation (38).

Gallium nitrate is rarely used because it has nephrotoxicity and its infusion takes 5 days continuously (3).

In conclusion, the first step of therapy in CIH patients is to restore renal function which is often impaired due to dehydration. Enhanced bone resorption represents the main cause of CIH and thus the second step is bisphosphonates administration. Bisphosphonates should be administered concurrently as the hypocalcemic effect starts within 2-4 days. Pamidronate, zoledronate and ibandronate are at present the main-stay of treatment. Calcitonin can be used given its prompt effect and favorable side-effect profile. Other non-bisphosphonates drugs have limited activity and several side-effects. Patients with refractory hypercalcemia should be considered for denosumab therapy and lastly for hemodialysis (Table 3).

Table 3: Therapeutic options for the management of Cancer induced Hypercalcemia.

Agent	Mechanisms of action	Cautions	Onset of action	Duration	Side effects
Normal saline (0.9% Sodium chloride) 200-400ml/hr 2-4 L IV/day	Volume repletion, increased renal Ca2+ clearance	Consider lower rate in patients with underlying renal disease	Immediate	2-3 days	Volume overload, non-aniongap metabolic acidosis
Calcitonin 4-8 units/kg SQ q 6-12 hours	Inhibits bone resorption, augments Ca++ excretion	Rebound ↑Ca2+ after 24 hours, vomiting, cramps, flushing, Rapid ↑Ca2+ within 2 to 6 hours	4-6 hours	Up to 3 days	Nausea, rhinitis, hypersensitivity reactions
Bisphosphonates Zoledronic acid 4mg administered IV over 15 min; Pamidronate 60-90mg administered IV over 2-24 h; Ibandronate 2-6 mg administered IV over 1-2 h	Inhibition of osteoclast activity, osteoclast apoptosis and improved osteoblast survival	Zoledronic acid: Do not use in patients with creatinine >4.5 mg/dl; no need for hepatic adjustment Pamidronate and ibandronate: Do not use if glomerular filtration rate is <30; no need for hepatic adjustment	Within 2-4 days after administration. Can be repeated after 7 days	3-4 weeks	Flu-like symptoms, nephrotic syndrome, acute kidney injury, osteonecrosis of the jaw
Denosumab 120mg SQ weekly for 4 weeks, then monthly thereafter	Impairs osteoclast activity	No need for renal and hepatic adjustment. Consider half dose for patients with renal disease to decrease the risk of hypocalcemia	Within 2-4 days after administration. Can be repeated after 7 days	3-4 months	Bone pain, nausea, diarrhea, shortness of breath, osteonecrosis of the jaw

1.6. Objectives of the study

1.6.1. Broad Objective

The broad objective of the study was to describe the management of hypercalcemia in patients with malignancies receiving Radiation therapy at CMJAH, Johannesburg from January 2012 to December 2015.

1.6.2. Specific objectives

The specific objectives/endpoints of this study were;

1. To study the incidence of types of malignancies associated with hypercalcemia and its correlation with stage of disease in patients receiving Radiation therapy at CMJAH, Johannesburg from January 2012 to December 2015.
2. To describe the treatment strategies used for hypercalcemia in cancer patients receiving radiation therapy at CMJAH, Johannesburg from January 2012 to December 2015.
3. To assess the effectiveness of bisphosphonates in control of Hypercalcemia in cancer patients receiving Radiation therapy at CMJAH, Johannesburg from January 2012 to December 2015.
4. To assess the toxicity of treatment with bisphosphonates in cancer patients receiving radiation therapy at CMJAH, Johannesburg from January 2012 to December 2015.

CHAPTER TWO

2.0. Materials and methods

2.1. Study design

This was a retrospective descriptive study; all cancer patients with hypercalcemia who were admitted at the Radiation oncology ward CMJAH for hypercalcemia management from January 2012 to December 2015 were included in the study and the data was collected by reviewing hospital folders from the hospital archives. The relevant information from files was recorded on a data collection form (proforma).

2.2. Study site/area

This study was conducted in the Radiation oncology department/ward at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH). CMJAH is an accredited central tertiary care academic hospital with 1088 beds serving patients from across the Gauteng province and neighboring provinces. It is estimated to have more than 4000 professional and support staff offering a full range of specialized services to inpatients and outpatients.

It is located in Parktown and serves as a referral hospital for a number of hospitals in its referral chain. The hospital is also a major teaching hospital for The University of the Witwatersrand, Faculty of Health Sciences for undergraduate and post-graduate training in all areas of health professions (36).

Radiation oncology department of the CMJAH is the only radiation center owned by state in Johannesburg, and it acts as a referral center for all hospitals in Johannesburg. Radiation Oncology Unit is the largest in the country and treats about 3 500 patients a year (36).

2.3. Study population

The study reviewed medical records of all cancer patients with hypercalcemia admitted to the Radiation oncology ward at Charlotte Maxeke Johannesburg Academic hospital from January 2012 to December 2015 and assessed for eligibility criteria.

2.4. Inclusion criteria

The study included medical records of cancer patients with hypercalcemia admitted to the Radiation oncology ward at CMJAH from January 2012 to December 2015.

Inclusion criteria:

1. Diagnosis of malignancy
2. Hypercalcemia, corrected calcium > 2.56mmol/l
3. Patient receiving or received radiotherapy

Exclusion criteria:

1. Age below 18 and Above 70 years
2. Patients that never received radiotherapy

2.5. Sampling and sample size

All patients admitted in the Radiation Oncology ward CMJAH for the management of hypercalcemia were included in the study.

A total number of 125 patients' files for the period of 4 years from January 2012 to December 2015 were available for review.

2.6. Data Management

2.6.1 Data collection

Each file was given a code according to the order of admission, and this code was used to link the data entered into the Excel sheet, and identifying details were removed so that the data remained anonymous and confidential.

The following data were collected from the patients' records: demographic information, Primary cancer diagnosis, stage, its presentation and treatment of primary tumor, presence of bone metastasis, clinical presentation, investigations done, pretreatment serum

(baseline) corrected Ca2+, and treatment of hypercalcemia given. Data on the outcome after treatment were also recorded, including 1 week and month post treatment corrected Ca2+, symptom relief, relapse and subsequent treatment given after relapsed. Information on type of hypercalcemia treatment given and its toxicity were also recorded.

The above information was recorded using data collection form (see Appendix A).

2.6.2. Data analysis

Participants' information was captured into an MS-Excel spread sheet. Data cleaning was done to check for missing values, any inconsistencies, and to identify any extreme values. After data cleaning, the MS-Excel spreadsheet was then imported to statistical software (SPSS_version 23) IBM, Armonk, NY for descriptive analysis purposes. Standard statistical methods were used. Categorical data was described using frequencies and percentages. The distribution of continuous variables was determined. These were then described using measures of central tendency: mean ± standard deviation for normally distributed data; and median and interquartile range for skewed data. A P-value of less than 0.05 was considered significant.

2.7. Ethical Consideration

Ethics approval was obtained from the Human Ethics Research Committee of the University of the Witwatersrand, which issued certificate number M140546 (see Appendix B). Institutional approval was obtained from the Chief Executive Officer of CMJAH (see Appendix C).

Only serial numbers were used to all patients' files reviewed in the study to maintain confidentiality.

CHAPTER THREE

3.0. Results

3.1. Descriptive analysis

3.1.1. Demographic characteristics of the study participants.

A retrospective chart review was conducted over a period of four years and a total number of 125 cancer patient records admitted for management of hypercalcemia from January 2012 to December 2015 were retrieved.

Mean age was 52.31 years ± 11.388 SD, with the youngest patient being 28 years old and the oldest being 70 years (Table 4). Sixty three (50.4%) patients were male, and 62 (49.6%) were female (Table 5).

Table 4: Age

	Age (years)
Minimum	28
Maximum	70
Mean	52.31
Std. Deviation	11.388

Table 5: Sex

	Frequency	**Percentage (%)**
Male	63	50.4
Female	62	49.6
Total	125	100

3.1.2. Site of primary Cancer diagnosis

The most frequent site of primary cancer diagnosis in patients with hypercalcemia were gynecological malignancies 31(24.8%), head and neck 23(18.4%), prostate 19(15.2%), breast cancer 17(13.6%), gastrointestinal malignancies 12(9.6%), multiple myeloma 5(4%) and lung cancer 3(2.4%), (Table 6).

Table 6: Cancer diagnosis and relative prevalence of hypercalcemia

Diagnosis/ site	Number of patients	Percentages (%)
Lung cancers	3	2.4
Breast cancer	17	13.6
Head and neck cancers	23	18.4
Multiple myeloma	5	4.0
Gynaecological cancers	31	24.8
Prostate cancer	19	15.2
GIT malignancies	12	9.6
Others	15	12.0

3.1.3. Presentation of Cancer diagnoses

Most patients had metastatic disease 46(36.8%) and uncontrolled primary disease 32(25.6%) compared to primary controlled disease 47(37.6%), (Table 7).

Table 7: Presentation of Cancer diagnoses

Presentation	Number of patients	Percentage (%)
Primary controlled	47	37.6
Primary uncontrolled	32	25.6
Metastatic disease	46	36.8

3.1.4. Presence of Bone metastasis

Bone metastases were present in 51(41%) patients and absent in 74(59%) patients (Table 8).

Table 8: Presence of Bone metastasis

	Number of patients	Percentage (%)
Present	51	41
Absent	74	59

3.1.5. Clinical presentation of patients with hypercalcemia

All patients presented with symptoms related to hypercalcemia. The most frequent clinical symptoms were Neuromuscular 41(32.8%), nausea/vomiting 37(29.6%), Polyuria 20(16%), mental 16(12.8) and Polydipsia 9(7.2%), (Table 9).

Table 9: Clinical manifestations of hypercalcemia in patients receiving radiotherapy.

Clinical manifestations	Number of patients	Percentages (%)
Nausea/vomiting	37	29.6
Polyuria	20	16
Polydipsia	9	7.2
Constipation	2	1.6
Neuromuscular	41	32.8
Mental	16	12.8
Nil	0	0

3.1.6. Level of Haemoglobin

Most patients were anaemic with haemoglobin level of <10 g/dL 83 (66.4%) and 10.1 g/dL 41 (32.8%). Only 0ne patient (0.8%) had haemoglobin of >12 g/dL. (Table 10)

Table 10: Level of Haemoglobin

Haemoglobin (g/dL)	Number of patients	Percentage (%)
<10	83	66.4
10.1	41	32.8
>12	1	0.8

3.1.7. Level of Pre-treatment Calcium

Majority of patients had severe hypercalcemia with pre-treatment serum calcium level of > 2.9 mmol/L 77 (61.6%), patients who had serum Ca level between 2.71-2.89 mmol/L were 28 (22.4%) and those with 2.56-2.70 mmol/L were 20 (16%). Minimum pre-treatment serum Ca level was 2.61 mmol/L, maximum 3.97 mmol/L with a mean of 3.0715 +/- SD 0.34918 mmol/L (Table 11).

Table 11: Level of Pre-treatment Calcium

Pre-treatment Calcium (mmol/L)	Number of patients	Percentage (%)
2.56-2.70	20	16
2.71-2.89	28	22.4
≥2.9	77	61.6

3.1.8. Electrolyte and renal function tests

Serum sodium and potassium, both available for all patients, were Mean 137 mmol/L +/- 7.690 SD and 4.150 mmol/L +/- 0.4965 SD respectively. The mean urea and creatinine were 8.2323 mmol/L +/-3.6051 and 103.363.5 mmol/L +/-40.664 SD respectively (Table 12).

Table 12: Electrolyte and renal function tests

	Minimum	Maximum	Mean	Std. Deviation
HB	3.4	12.1	9.182	1.7931
Na2+	120	149	137.02	7.690
Ca2+	2.61	3.97	3.0689	0.35329
K+	3.2	5.2	4.150	0.4965
Urea	4.0	18.1	8.232	3.6051
Creatinine	48	265	103.36	40.664

3.2. Treatment and Outcome

3.2.1. Treatment modalities given

One hundred and four patients (83.2%) received hydration + bisphosphonates and 21(16.8%) of patients received hydration alone, non-received haemodialysis (Table 13). Zoledronic acid was the bisphosphonates used in 95% of patients.

Table 13: Treatment modalities given

Treatment	Number of patients	Percentage (%)
Hydration alone	21	16.8
Hydration +bisphosphonate	104	83.2
Haemodialysis	0	0
Other	0	0

Overall Improvement in calcium with hydration alone	Improvement in calcium with hydration + bisphosphonates.
At 1 week (p=0.00)	At 1 week (p=0.00)
At 1 month (p=0.00)	At 1 month (p=0.00)

3.2.2. Post treatment levels of Calcium

1 week post treatment majority of patients had ≤2.55 mmol/L Serum level of Calcium 81 (64.8%), 11 patients (8.8%) had serum level of calcium 2.56-2.71 mmol/L, 23 patients (18.4%) had serum calcium between 2.71-2.89 mmol/L and only 10 patients (8.0%) had serum level of calcium ≥ 2.9 mmol/L (Table 14). The corrected serum calcium was 2.4770 ± 0.34512 mmol/L one week after treatment.

1 month post treatment majority of patient's 99 (79.2%) remains to have normal serum level of calcium ≤ 2.55 and only about 11 (8.8%) patients had ≥ 2.9 mmol/L (Table 15).

Table 14: Post treatment level of calcium (1 week)

Calcium (mmol/L)	Number of patients	Percentage (%)
≤2.55	81	64.8
2.56-2.70	11	8.8
2.71-2.89	23	18.4
≥2.9	10	8.0

Table 15: Post treatment level of calcium (1 month)

Calcium (mmol/L)	Number of patients	Percentage (%)
≤2.55	99	79.2
2.56-2.70	12	9.6
2.71-2.89	3	2.4
≥2.9	11	8.8

3.2.3. Symptom relief

Most patients had symptoms relief after the treatment 93 (74.4%) after one week and 115 (92%) after 1 month (Table 16).

Table 16: Symptom relief

	No. at 1 week (%)	**No. at 1 month (%)**
Yes	93 (74.4)	115 (92)
No	32 (25.6)	10 (8)

3.2.4. Time to relapse after treatment

The time to relapse was between 3.28-56 days (mean 34.0518 +/- 12.28215 SD) after treatment of hypercalcemia (Table 17).

Table 17: Time to relapse

	Minimum	Maximum	Mean	Std. Deviation
Time to relapse (Days)	3.28	56.00	34.0518	12.28215

3.3. Treatment of primary malignancy

Majority of patients were receiving Radiation alone 72 (57.6%) as sole treatment modality for their primary cancer. Thirty seven (29.6%) patients were receiving chemotherapy then Radiotherapy and 15 (12.0%) concurrent chemo-radiation therapy (Table 18).

Table 18: Treatment of primary malignancy

Treatment	**Number of patients**	**Percentage (%)**
Radiation	72	57.6
Surgery +radiation	1	0.8
Chemotherapy then RT	37	29.6
Conc. Chemo+radiation	15	12.0

3.4. Toxicities to bisphosphonates

Side effects to bisphosphonates were mainly gastrointestinal: Nausea/vomiting 42 (33.6%) patients, Constipation 14 (11.2%), abdominal pain 13 (10.4), Diarrhoea 11 (8.8) and anorexia 1 (0.8) patients. Other toxicities reported were fever 12 (9.6%) patients and hypocalcemia 14 (11.2%). Eighteen patients (14.4%) did not report any side effect to treatment (Table 19).

Table 19: Toxicities to bisphosphonates

Toxicity	Number of patients	Percentage (%)
Nil	18	14.4
Fever	12	9.6
Nausea/vomiting	42	33.6
Constipation	14	11.2
Diarrhoea	11	8.8
Abdominal pain	13	10.4
Anorexia	1	0.8
Hypocalcemia	14	11.2

3.5. Treatment versus Pre-treatment Calcium level

Fourteen (58%) patients with pre-treatment calcium level of 2.56-2.70 mmol/L received hydration alone and 76 (98%) of patients with serum pre-treatment calcium of ≥ 2.9 mmol/L were treated with hydration + bisphosphonates (P=0.00) (Table 20).

Table 20: Treatment versus pre-treatment Calcium level

Calcium level (mmol/L)	**2.56-2.70**	**2.71-2.89**	**≥2.9**	**Total**
Hydration	14	6	1	21
Hydration+ bisphosphonates	10	18	76	104
Total	24	24	77	125
				P=0.00

3.6. Diagnosis versus pre-treatment calcium level

Table 21: Diagnosis versus pre-treatment calcium level

Site	**2.56-2.70 mmol/L**	**2.71-2.89 mmol/L**	**≥2.9 mmol/L**	**No. of patients**
Lung	0	0	3	3
Breast	4	2	11	17
Head and Neck	8	6	9	23
Multiple Myeloma	2	2	1	5
Gynae	3	3	25	31
Prostate	2	6	11	19
GIT	2	2	8	12
Others	3	3	9	15
				P=0.174

CHAPTER FOUR

4.0. Discussion

This was a retrospective descriptive study, 125 patients who were admitted at the Radiation oncology ward CMJAH for hypercalcemia management from January 2012 to December 2015, were analysed.

Mean age was 52.31 years ± 11.388 SD, with the youngest patient being 28 years old and the oldest being 70 years. Male and female ratio was 1:1.

The most frequent site of primary cancer diagnosis in patients with hypercalcemia in our study were gynaecological malignancies (24.8%), head and neck (18.4%), prostate (15.2%), breast cancer (13.6%), gastrointestinal malignancies (9.6%), multiple myeloma (4%) and lung cancer (2.4%). The literature states that Lung cancer, breast cancer and multiple myeloma have the highest incidence of CIH, accounting for more than 50%, while the disease occurs rarely in patients with colorectal and prostate cancer (8, 9). This differs from our study were gynaecological, head and neck, prostate and breast cancer were the leading causes of CIH, followed by GIT, multiple myeloma and Lung. At CMJAH haematological malignancies, metastatic breast and lung are primarily managed by Medical oncology unit, which is separated from radiation oncology unit. This can explain the lower number of lung, metastatic breast and multiple myeloma in our findings.

Most patients in our study had metastatic disease (36.8%) and uncontrolled primary disease (25.6%) compared to primary controlled disease (37.6%). Bone metastases were present in (41%) patients. This correspond with the literature which shows Cancer induced hypercalcemia (CIH) is particularly common in patients with advanced cancer and is an indicator of poor prognosis with a mean survival rate of 2-3 months except in patients with multiple myeloma and breast cancer (3, 11). The extent of metastatic bone disease correlates poorly with both the occurrence and severity of CIH (46).

All patients presented with symptoms related to hypercalcemia. Majority of patients had severe hypercalcemia with pre-treatment serum calcium level of > 2.9 mmol/L (61.6%) and the mean serum calcium level was 3.0715 mmol/L. The finding in our study that all patients were symptomatic is likely because of their higher serum calcium levels. This is supported by the medical literature that states that serum calcium levels exceeding 3.0 mmol/L are often symptomatic (2).

Neuromuscular symptoms were the leading symptom for hypercalcemia, followed by nausea/vomiting, polyuria, mental and polydipsia. Nausea and anorexia were the second leading symptoms, which are also well described in the medical literature as symptoms of hypercalcemia (43).

Most patients in our study were anaemic with haemoglobin level of <10 g/dL 83 (66.4%), only one patient (0.8%) had haemoglobin of >12 g/dL. This can be explained by their chronic and advanced malignant diseases.

A significant proportion of patients with Cancer induced hypercalcemia had concurrent other electrolyte disorders in the literature. Cancer induced Hypercalcaemia patients had increased serum urea and creatinine levels, a higher urea/creatinine ratio, and a higher rate of acid-base disorders, but lower serum albumin, potassium, chloride, phosphorus, and magnesium concentrations than those found in the control subjects (45). Our results showed serum sodium and potassium were Mean 137 mmol/L +/- 7.690 SD and 4.150 mmol/L +/- 0.4965 SD. The mean urea and creatinine were 8.2323.5 mmol/L +/-3.6051 and 103.363.5 mmol/L +/-40.664 SD respectively which did not match with the literature.

In our study, all patients received standard therapy for acute hypercalcemia. Patients with higher serum calcium received more calcium lowering agents, and non-received haemodialysis. One hundred and four patients (83.2%) received hydration + bisphosphonates and 21(16.8%) of patients received hydration alone. Fifty eighty percent of patients with pre-treatment serum calcium of ≤2.70 mmol/L received hydration alone and (98.7%) of patients with pre-treatment serum calcium level of ≥2.9 mmol/L received hydration + bisphosphonates as a treatment modality (p=0.00). Zoledronic acid was used in 95% of patients who received hydration + bisphosphonates as mode of treatment.

The response to treatment after one week was (73.6%) patients and (88.8%) after one month. The mean corrected serum calcium was 2.5 mmol/L one week after treatment (P=0.00). This correspond with the literature that 70-100% response rates in CIH patients who were treated with hydration + bisphosphonates (47, 48, 49). Most patients had symptoms relief (74.4%) one week and (92%) one month after treatment.

The time to relapse in this study was 34 days after treatment of hypercalcemia, similar to the time to relapse of zoledronic acid 30-40 days (50).

Majority of patients were receiving Radiation alone (57.6%) as sole treatment modality for their primary cancer. Thirty seven (29.6%) patients were receiving chemotherapy and (12.0%) concurrent chemo-radiation therapy.

Side effects to bisphosphonates were mainly gastrointestinal: Nausea/vomiting (33.6%) patients, Constipation (11.2%), abdominal pain (10.4%), Diarrhoea (8.8%) and anorexia (0.8%) patients. Other toxicities reported were fever (9.6%) patients and hypocalcemia (11.2%). Eighteen patients (14.4%) did not report any side effect to treatment. Our results correspond to toxicities of bisphosphonates most reported in the literature (28).

4.1. Study limitations

The limitations of this study include

- It is a single centre study conducted in a radiation oncology ward so the results may not be representative of all oncology units.
- It is a retrospective study.
- There is non-standardized documentation (all signs and symptoms of hypercalcemia were likely not documented for each patient).

4.2. Conclusion

Hypercalcemia of malignancy remains to be a common finding in patients with advanced stage cancers. The most frequent site of primary cancer diagnosis in patients with hypercalcemia in our study were gynaecological malignancies, head and neck, prostate, breast cancer, gastrointestinal malignancies, multiple myeloma and lung cancer.

Hypercalcemia of malignancy usually presents with markedly elevated calcium levels and patients are therefore usually symptomatic.

Our results show that in patients with malignancy induced hypercalcemia presents with symptoms such as neuromuscular symptoms, gastrointestinal symptoms such as nausea or disorientation, or a change in mental status.

For acute management of hypercalcemia, rehydration is the mainstay of treatment because all patients tend to have dehydration. Bisphosphonates are potent calcium lowering agents, but they are contraindicated in patients with declined renal function.

In our study, all patients received standard therapy for acute hypercalcemia. Patients with higher serum calcium received calcium lowering agents. Ninety two patients (73.6%) responded to treatment after one week and 111 (88.8%) patients remains to have normal serum one month after treatment.

Common bisphosphonates toxicities noted were mainly gastrointestinal: Nausea/vomiting, constipation, abdominal pain, diarrhoea and anorexia. Other toxicities reported were fever and hypocalcaemia.

4.3. Recommendations

- Emergency physicians/ oncologists should measure serum calcium and albumin levels in all patients with underlying malignancy present with unspecific symptoms such as weakness, gastrointestinal symptoms such as nausea or disorientation, or a change in mental status.
- Hypercalcemic crisis is a life-threatening emergency. Aggressive IV hydration and bisphosphonate therapy should be used in management of symptomatic CIH or patient with a serum calcium level of > 2.56 mmol/L to alleviate the clinical manifestations of hypercalcaemic disorders.
- Patients with advanced underlying kidney disease and refractory severe hypercalcemia should be considered for denosumab therapy and haemodialysis.

Appendix A: Proforma (Data collection form)

<table>
<tr><td colspan="10">PROFORMA</td></tr>
<tr><td>Code number</td><td colspan="9"></td></tr>
<tr><td>Suitability</td><td colspan="4">1= Yes</td><td colspan="5">2= No</td></tr>
<tr><td>Age (years)</td><td colspan="9"></td></tr>
<tr><td>Sex</td><td colspan="4">1= Male</td><td colspan="5">2= Female</td></tr>
<tr><td>Diagnosis of malignancy</td><td>1= Lung</td><td>2= Breast</td><td>3= Head and neck</td><td>4= Multiple Myeloma</td><td>5= Gynae</td><td>6=Prostate</td><td>7= GIT</td><td colspan="2">8= Others</td></tr>
<tr><td>Presentation of primary cancer</td><td colspan="2">1= Primary Controlled</td><td colspan="2">2= Primary Uncontrolled</td><td colspan="5">3= Metastatic disease</td></tr>
<tr><td>Bone Metastasis</td><td colspan="3">1= Present</td><td colspan="6">2= Absent</td></tr>
<tr><td rowspan="3">Clinical presentation</td><td colspan="3">1= Nausea & Vomiting</td><td colspan="3">2= Polyuria</td><td colspan="3">3= Polydipsia</td></tr>
<tr><td colspan="3">4 = Constipation</td><td colspan="3">5= Neuromuscular</td><td colspan="3">6= Mental</td></tr>
<tr><td colspan="3">7= Nil</td><td colspan="3"></td><td colspan="3"></td></tr>
<tr><td>Investigations done</td><td>HB</td><td>Na^{2+}</td><td>K^{+}</td><td>Ca^{2+}</td><td>Urea</td><td>Creatinine</td><td colspan="3"></td></tr>
<tr><td>Pre-treatment serum (baseline) corrected Ca in mmol/l</td><td colspan="9"></td></tr>
</table>

Treatment of Hypercalcaemia	1= Hydration alone	2= Hydration + Bisphosphonates	3= Hydration + Steroids
1 week post treatment corrected Ca^{2+} (mmol/l)			
1 month post treatment corrected Ca^{2+} (mmol/l)			
Symptom relief at 1 week	1= Yes	2= No	
Symptom relief at 1 month	1= Yes	2= No	
Relapse	1= Yes	2= No	
Time to relapse (days)			
Subsequent treatment after relapse	1= Hydration Alone	2= Hydration + Bisphosphonates	3= Hydration + Steroids

Treatment of Primary tumour	1= Surgery	2= Radiation	3= Surgery + Radiation	4= Chemo Then RT	5. Concurrent ChemoRT

Acute toxicity (Side effects) of Bisphosphonates	0= Nil	1= Fever	2= Nausea &Vomiting
	3= Constipation	4= Dyspnoea	5= Diarrhoea
	6= Abdominal pain	7= Anorexia	8= Hypocalcaemia
	9= Others		

Appendix B: Ethic clearance certificate- Medical, from ethics committee

M140546

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M140546

NAME: (Principal Investigator)	Dr Jerry Ndumbalo
DEPARTMENT:	Department of Radiation Oncology CM Johannesburg Academic Hopspital
PROJECT TITLE:	Incidence and Treatment of Hypercalcaemia in Cancer Patients Receiving Radiation: A Retrospective Review of Practice at Charlotte Maexeke Johannesburg Academic Hospital from January 2012-June 2013
DATE CONSIDERED:	30/05/2014
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof Vinay Sharma

APPROVED BY: _____

Professor PE Cleaton-Jones, Chairperson, HREC (Medical)

DATE OF APPROVAL: 30/05/2014

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House University.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned researc and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from th research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit yearly progress report**.

_____ _____

Principal Investigator Signature M140546Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix C: CMJAH CEO letter of approval

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

Enquiries:
Ms. O. Noge
Office of the Chief Executive Officer
Tell: 011 488 3792
Fax: 011 488 3793
Email:Lindiwe.Mngomezulu@gauteng.gov.za
Date: 25th April 2014

Dr. Jerry Ndumbalo
Department of Radiation Oncology
CMJAH

Dear Dr. Ndumbalo

RE: "Incident and treatment of Hypercalcemia in Cancer patients receiving radiation – a Retrospective review of practice at CMJAH from Jan 2012 – June 2013"

Please note that permission to conduct the above mentioned study is provisionally approved. Your study can only commence once ethics approval is obtained. Please forward a copy of your ethics clearance certificate as soon as the study is approved by the ethics committee for the CEO's office to give you the final approval to conduct the study.

Approved/not approved

Ms. G. Bogoshi
Chief Executive Officer
Date: 30/04/2014

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