RESEARCH ARTICLE

Impact of Chemotherapy on Hypercalcemia in Breast and Lung Cancer Patients

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Abstract

Introduction: Hypercalcemia is mainly caused by bone resorption due to either secretion of cytokines including parathyroid hormone-related protein (PTHrP) or bone metastases. However, hypercalcemia may occur in patients with or without bone metastases. The present study aimed to describe the effect of chemotherapy treatment, regimens and doses on calcium levels among breast and lung cancer patients with hypercalcemia. Methods: We carried a review of medical records of breast and lung cancer patients hospitalized in years 2003 and 2009 at Penang General Hospital, a public tertiary care center in Penang Island, north of Malaysia. Patients with hypercalcemia (defined as a calcium level above 10.5 mg/dl) at the time of cancer diagnosis or during cancer treatment had their medical history abstracted, including presence of metastasis, chemotherapy types and doses, calcium levels throughout cancer treatment, and other co-morbidity. The mean calcium levels at first hospitalization before chemotherapy were compared with calcium levels at the end of or at the latest chemotherapy treatment. Statistical analysis was conducted using the Chi-square test for categorical data, logistic regression test for categorical variables, and Spearman correlation test, linear regression and the paired sample t tests for continuous data. Results: Of a total 1,023 of breast cancer and 814 lung cancer patients identified, 292 had hypercalcemia at first hospitalization or during cancer treatment (174 breast and 118 lung cancer patients). About a quarter of these patients had advanced stage cancers: 26.4% had mild hypercalcemia (10.5-11.9 mg/dl), 55.5% had moderate (12-12.9 mg/dl), and 18.2% severe hypercalcemia (13-13.9; 14-16 mg/dl). Chemotherapy lowered calcium levels significantly both in breast and lung cancer patients with hypercalcemia; in particular with chemotherapy type 5-flurouracil+epirubicin+cyclophosphamide (FEC) for breast cancer, and gemcitabine+cisplatin in lung cancer. Conclusion: Chemotherapy decreases calcium levels in breast and lung cancer cases with hypercalcemia at cancer diagnosis, probably by reducing PTHrP levels.

Keywords: Hypercalcemia - PTHrP - chemotherapy type - breast cancer - lung cancer

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Introduction

Hypercalcemia is a life-threatening situation in which serum calcium level is elevated above 10.5 mg/dl, while albumin concentration is lower than 4 g/dl. Hypercalcemia occurs in about 10%-20% of all cancer patients, especially among patients with lung, breast, and head and neck cancers. In hematological cancer, the incidence of hypercalcemia is commonly seen in the advanced phase of multiple myeloma and lymphomas. Hypercalcemia causes significant morbidity and mortality in particular among breast cancer patients (Mundy, 1990; Wysolmerski and Broadus, 1994; Ericson, 1999; Helft et al., 1999; Swartout-corbeil, 2002; Dolan, 2005; Swartout-corbeil, 2005).

Hypercalcemia can occur in cancer patients with and without bone metastasis. In patients with bone metastasis (i.e., extensive localized bone destruction), hypercalcemia is kwon as local osteolytic hypercalcemia (LOH) (Mundy, 1990; Wysolmerski and Broadus, 1994; Ericson, 1999; Helft et al., 1999; Swartout-corbeil, 2002; Dolan, 2005; Swartout-corbeil, 2005), and effects mainly breast cancer patients.

In cancer patients without bone metastasis, hypercalcemia is caused by the pathological bone resorption due to the secretion of cytokines, including parathyroid hormone-related protein (PTHrP), leading to activation and differentiation of osteoclast cells. PTHrP levels are also associated with the onset of hypercalcemia in breast cancer patients without bone metastases (Henderson et al., 2006).

PTHrP level is considered as a critical factor in

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the onset of hypercalcemia in both local osteolytic hypercalcemia (LOH) and humoral hypercalcemia of malignancy (HHM) cancer group. PTHrP is a hormone produced by tumor cells especially in LOH type. Massive production of PTHrP will lead to hypercalcemia, as its biological action is similar to PTH, as PTHrP will bind to the same receptors. PTHrP will increase with increase in cell proliferation, differentiation and tumor enlargement (Oda et al., 1998; Tovar et al., 2002). Thus cancer chemotherapy may prevent or reduce hypercalcemia by decreasing cell proliferation and tumor growth.

The present study aims to determine whether chemotherapy treatment, regimens and doses affects calcium levels, hypercalcemia onset and severity among breast and lung cancer patients.

Materials and Methods

Study design and setting

We performed a retrospective observational study at Penang General Hospital which is located in the state of Penang Island, Malaysia. Penang Hospital is the largest public hospital in north Malaysia and it is a referral center for cancer patients. The ethical approval for the study was obtained from Clinical Research Centre (CRC) of the, Ministry of Health Malaysia (MOH).

Patients

Patients admitted to Penang Hospital between 2003 to 2009 were considered as eligible for this study if they were aged 18 years or above, had a primary or advanced breast or lung cancer diagnosis regardless of stage, had clinically and laboratory diagnosed hypercalcemia (calcium level above 10.5 mg/dl or greater than 2.5 mmol/L) at cancer diagnosis or during cancer treatment, and had a normal or almost normal ALT, AST and serum total bilirubin.

Patients were considered ineligible if they had used thiazides diuretics or calcitonin within the last 7 days, had a diagnosis of hyperparathyroidism, hyperthyroidism, adrenal insufficiency, renal impairment or failure, or any other concomitant cancer diagnosis (hematological malignancy such as multiply myeloma, Non-Hodgkin lymphoma or Hodgkin lymphoma or Lymphoma or thyroid or kidney cancer) (Drug Lib COM., 2010; World Health Organization, 2010).

Data collection

The information was abstracted from medical records using a standardized data abstraction form. The variables abstracted were: age, gender, ancestry (Chinese, Malay, Indian), type of cancer, cancer stage, presence of metastases, use of chemotherapy, type of chemotherapy, number of chemotherapy cycles, chemotherapy doses in each cycle, and information related with use of bisphosphonates, furosemide and hydration for hypercalcemia treatment. Information on calcium levels was collected at the time of cancer diagnosis before chemotherapy and, for those who had hypercalcemia, information on calcium levels was collected again after three weeks at regular medical follow-up visit (after chemotherapy). Hypercalcemia severity was classified according to calcium levels as mild (Ca=10.5-11.9 mg/dl), moderate (Ca=12-12.9 mg/dl) and severe (Ca=13-13.9 mg/dl).

Statistical analysis

Types of chemotherapy regimens, presence and severity of hypercalcemia, and presence of metastases were considered as categorical variables.

The total doses of chemotherapeutic treatment were considered as continuous variables.

Data analysis was performed with by the Statistical Package of Social Science (SPSS®) software program version 15.

The distribution of categorical variables was tested, using a parametric test (Chi-square).

The level of significance for associations was set at $P < 0.05$. Further, logistic regression was used to estimate odd ratio (OR) and 95% confidence intervals (CI) for association between different types of chemotherapeutics regimens and hypercalcemia. For continuous data, Spearman correlation test was used when the data was not normally distributed, as assessed by Kolmogorov-Smirnov test. For data which showed significant correlation, Linear regression was used in order to find the strongest correlation and association between of chemotherapy drugs doses with hypercalcemia onset and severity. The Paired Samples t Test is used to detect the differences between calcium level before and after the uses of chemotherapy treatment

Results

Patient characteristics

A total of 1023 breast and 814 lung cancer patients were diagnosed and treated in the Penang general hospital during the study period. Among these, 292 patients had hypercalcemia at cancer diagnoses or during cancer treatment: 209 were female (71.6%) and 83 male (28.4%); 174 patients had breast cancer (59.6%), and 118 lung cancer (40.4%).

Among the 174 breast cancer patients with hypercalcemia, 11 had stage I (6.9%), and 43 had stage II (24.7%), 77 had stage III (44.3%), and 43 had stage IV (24.7%). Among the 118 lung cancer patients with hypercalcemia, 11 had stage I (6.9%), 25 had stage II (21.2%), 47 has stage III (39.8%), and 29 had stage IV (24.6%). Most of the patients were of Chinese ancestry (n=151; 51.7%), followed by Malay (n=112; 38.4%) and Indian (n=29; 9.9%) ancestries.

The mean age at first hospitalization for cancer was 52.2 years (range, 22-83 years), most patients (n=109; 37.3%); were aged between 50-59 years.

Prevalence of hypercalcemia

Of the 292 patients with hypercalcemia, the majority had the condition diagnosed at the same time of cancer diagnosis (n=189; 64.7%); 103 (35.3%) patients had hypercalcemia diagnosed after 3 weeks of cancer diagnosis, when all the patients were retested.

Seventy seven (26.4%) had mild hypercalcemia (Ca= 10.5-11.9 mg/dl), 162 (55.5%) moderate hypercalcemia

(Ca= 12-12.9 mg/dl), and 53 (18.2%) severe hypercalcemia. Among the patients with severe hypercalcemia 21 (7.2%) had calcium level between 13-13.9 mg/dl, and 32 (11%) had calcium level between 14-16 mg/dl.

Hypercalcemia treatment

Patients with hypercalcemia were treated with pamidronate plus normal saline solution (n=135; 46.2%), zoledronic acid plus normal saline solution plus furosemide (n=57; 19.5%), only normal saline solution (n=39; 13.4%). A smaller proportion of the patients were with the combination of pamidronate plus normal saline plus furosemide (n=33; 11.3%) or with with zoledronic acid plus normal saline plus furosemide (n=28; 9.6%).

Metastases

The majority of the breast (75.3%) and lung (75.4%) cancer patients did not have metastases. Among the 43 (24.7%) breast cancer patients who had metastasis, 32 (18.4%) were in bone, 6 (3.4%) in the lung, 3 (1.7%) in the brain metastasis and 2 (1.1%) in the liver. Among the 29 (24.6%) lung cancer patients who had metastasis, 21(17.8%) were in bone, 3 (2.5%) in the lungs, 2 (1.7) in the brain, 2(1.7%) in the liver and 1(0.8) in the kidney. Thus, among those who did developed metastasis for both breast and lung cancers, bone metastasis was the most common type.

Chemotherapy types and doses

Among the breast and lung cancer patients included in the study, the most common types of chemotherapeutics regimens used were: (5-flururacil, epirubicin and cyclophosphamide) (FEC) (101; 34.6%), gemcitabine and

Table 1. Chemotherapy Types and Doses Received By 174 Breast and 118 Lung Cancer Patients With Hypercalcemia

All Patients		Chemotherapy Doses		Breast		Lung	
		N	%	N	%	N	%
5-FU	700-799 mg	4	0.7	4	0.7		
	800-899 mg	28	4.6	28	4.6		
	900-999 mg	32	5.2	32	5.2		
	≥1000 mg	37	6	37	6		
Epirubicin	80-89 mg	21	3.4	21	3.4		
	90-99 mg	38	6.2	38	6.2		
	≥100 mg	42	6.9	42	6.9		
Cyclophosphamide							
	700-799 mg	4	0.7	4	0.7		
	800-899 mg	28	4.6	28	4.6		
	900-999 mg	32	5.2	32	5.2		
	≥1000 mg	37	6	37	6		
Cisplatin	90-99 mg	41	6.7			41	6.7
	≥100 mg	77	12.6			77	12.6
Gemcitabine	1000-1200 mg	36	5.9			36	5.9
	>1200 mg	55	8.9			55	8.9
Etoposide	120-130 mg	10	1.6			10	1.6
	>130 mg	17	2.8			17	2.8
Docetaxel	100-110 mg	34	5.6	34	5.6		
	>110 mg	39	6.4	39	6.4		
Total		612	100				

Table 2. Effect of Chemotherapy Regimens on the Size of 174 Breast and 118 Lung Cancer Tumor and Metastasis (cancer size depend on cT= clinical staging)

	N	Improvement in Cancer size		
		1st cycle	3rd cycle	4th-5th cycle
FEC on breast cancer				
(Stage I, cT_1)	7	(1.6-2)	cancer responding size start to reduce	Ca size reduced at lest (1 cm)
(Stage II, cT_2)	23	(2.2-4.7)	--*	--*
(Stage III, cT_3)	45	(5.1-7.6)	--*	--*
(Stage IV, cT_4)	26	Metastasis to different sites	few cancer metastasis start to disappear from its metastasis site	some of Ca metastasis disappear
	N	1st cycle	4th-5th cycle	6th cycle
Docetaxel on Breast cancer				
(Stage I, cT_1)	4	(1.7-1.9)	cancer responding size start to reduce	Ca size reduced at lest (1)
(Stage II, cT_2)	20	(2.1-4.9)	--*	--*
(Stage III, cT_3)	32	(5-8)	--*	--*
(Stage IV, cT_4)	17	Metastasis to different sites	few start to disappear	some of Ca metastasis disappear
	N	1st cycle	3rd cycle	5th cycle
Gemcitabine+cisplatin on lung cancer				
(Stage I, cT_1)	10	(1.9- 2.7)	cancer responding size start to reduce	Ca size reduced at lest (1)
(Stage II, cT_2)	21	(3- 4.6)	--*	--*
(Stage III, cT_3)	35	any size but invades chest wall or diaphragm	few invades start to disappear	some of Ca invades start to disappear
(Stage IV, cT_4)	25	any size but metastasis to different sites	few of cancer metastasis start to disappear	some of Ca metastasis disappear
	N	1st cycle	4th-5th cycle	6th cycle
Etoposide +cisplatin on lung cancer				
(Stage I, cT_1)	3	(2-2.9)	cancer responding size start to reduce	Ca size reduced at lest (1)
(Stage II, cT_2)	4	(3-4.1)	--*	--*
(Stage III, cT_3)	13	any size but invades chest wall or diaphragm	few invades start to disappear	some of Ca invades start to disappear
(Stage IV, cT_4)	7	any size but metastasis to different sites	few of cancer metastasis start to disappear	some of Ca metastasis disappear

*same result as above, Ca: cancer.

Table 3. Effect of Chemotherapy on Calcium Levels of Breast and Lung Cancer with Hypercalcemia (HC)

	N	Mean Ca level chemotherpy			
		Before	After		
			1st cycle	3rd cycle	4th-5th cycle
		(mg/dl)	(mg/dl)	(mg/dl)	(mg/dl)
FEC on breast cancer					
Calcium level					
Mild HC	27	(11.3)	(11.1)	(10.5)	10.3-10.6 (10.4)
Moderate Hc	51	(12.7)	(12.5)	(11.8)	10.4-10.7 (10.5)*
Severe HC	23	(14.4)	(14.0)	(12.3)	10.5-11.1 (10.8)*
	N		1st cycle	4th-5th cycle	6th cycle
		(mg/dl)	(mg/dl)	(mg/dl)	(mg/dl)
Docetaxel on breast cancer					
Mild HC	19	(11.1)	(11.0)	(10.8)	10.4-10.7 (10.55)
Moderate Hc	42	(12.5)	(12.3)	(11.9)	10.6-10.8 (10.6)*
Severe HC	12	(14.5)	(14.1)	(12.9)	10.7-11.2 (10.9)*
	N		1st cycle	3rd cycle	5th cycle
		(mg/dl)	(mg/dl)	(mg/dl)	(mg/dl)
Gemcitabine+cisplatin on lung cancer					
Mild HC	14	(11.2)	(11.0)	(10.6)	10.4-10.6 (10.5)
Moderate Hc	58	(12.8)	(12.6)	(11.8)	10.5-10.8 (10.6)
Severe HC	12	(14.5)	(14.3)	(12.5)	10.6-11.1 (10.85)
	N		1st cycle	4th-5th cycle	6th cycle
		(mg/dl)	(mg/dl)	(mg/dl)	(mg/dl)
Etoposide+cisplatin on lung cancer					
Mild HC	17	(10.9)	(10.8)	(10.7)	10.5-10.6 (10.55)
Moderate Hc	11	(12.3)	(12.2)	(11.8)	10.6-10.9 (10.75)
Severe HC	6	(15)	(14.9)	(13.3)	10.6-11.3 (10.95)

*keep reducing, Ca: calcium.

Table 4. Correlation of Chemotherapy Doses with Calcium Level

Variables		r	P*
5-FU Doses	700-799 mg	0.113	0.257
	800-899 mg	-0.663	0.011
	900-999 mg	-0.769	0.001
	≥1000 mg	-0.948	0
Epirubicin doses	80-89 mg	0.043	0.646
	90-99 mg	0.286	0.076
	≥100 mg	-0.334	0.048
Cyclophosphamide doses	700-799 mg	-0.373	0.752
	800-899 mg	-0.404	0.011
	900-999 mg	-0.821	0.003
	≥1000 mg	-0.957	0.001
Cisplatin doses	90-99 mg	0.544	0.013
	≥100 mg	-0.819	0.004
Docetaxel doses	100-109 mg	-0.414	0.028
	≥110 mg	-0.782	0.002
Gemcitabine doses	1000-1200 mg	-0.568	0.031
	>1200 mg	-0.701	0.009
Etoposide doses	120-130 mg	0.099	0.368
	>130 mg	-0.669	0.047

*Spearman Correlation test between calcium level and chemotherapy doses.

cisplatin combination (84; 28.8%), docetaxel (73; 25%), and etoposide and cisplatin combination (34; 11.6%). The doses of chemotherapeutical drugs used varied widely (Table 1). Generally most patients treated with the higher doses of the chemotherapy had hypercalcemia.

Chemotherapy effect on cancer size and metastases

The selection of chemotherapy agents, regimens and doses varied according to cancer type, stage, size and presence and localization of metastases.

Among the patients with breast cancer, those treated with FEC had a reduction of the breast cancer size and disappearance of the breast cancer metastasis more frequently than those treated with docetaxel.

Most patients treated with FEC had noticeable effect on tumor size by the 3rd cycle of chemotherapy, whereas for patients treated with docetaxel the apparent reduction in tumor size was noticeable after the 4th or 5th cycle. Similarly, reduction in the number of metastases, was noted at the 4th or 5th cycle of FEC, as compared to happened after the 6th cycle with docetaxel (Table 2).

Among lung cancer patients, treatment response was observed after the 3rd cycle of treatment with gemcitabine plus cisplatin, and after the 4th or 5th cycle for etoposide plus cisplatin. Reduction in the number of metastasis was noticeable after the 5th cycle of treatment with gemcitabine plus cisplatin, or the 6th cycle of treatment with etoposide plus cisplatin (Table 2).

Chemotherapy effect on calcium level

Among breast cancer patients, those treated with FEC had a higher reduction in calcium levels than those treated with docetaxel.

The start in the reduction of calcium levels was noticeable by the 3rd cycle of FEC chemotherapy, whereas this effect was noticeable after the 4th or 5th cycle of docetaxel chemotherapy (Table 3).

Among lung cancer patients, hypercalcemia treatment response was observed after the 3rd cycle of treatment with gemcitabine plus cisplatin, and after the 4th or 5th cycle for etoposide plus cisplatin (Table 3).

There was an association between type of chemotherapy and the onset and severity of hypercalcemia (P=0.00). There was an association between type of chemotherapy, and cancer stages (P=0.001) and presence of metastasis (P=0.000).

Cyclophosphamide ≥ 1000 mg have the strongest association and highest negative correlation with calcium level decreases, followed by 5-FU ≥1000 mg, and cyclophosphamide 900-999 mg dose, 5-FU 900-999 mg dose, docetaxel dose ≥110 mg, cisplatin dose ≥100 mg, gemcitabine dose >1200 mg and cisplatin dose 90-99 mg (Table 4).

Calcium levels before chemotherapy were statistically significantly different than calcium level after chemotherapy (the Paired t Test P=0.003), indicating that chemotherapy has reduces calcium levels among patients with hypercalcemia.

Discussion

In our present study the majority of breast and lung cancer patients with hypercalcemia had stages I and III.

Among breast cancer patients, FEC regimen reduced calcium level, as well as tumor size and metastasis than docetaxel. Among lung cancer patients, gemcitabine plus cisplatin had detectable effects on tumor size and calcium levels already in the 3rd cycle of chemotherapy, while effects were observed treatment with etoposide plus cisplatin in the 4th and 5th cycles. Among patients with hypercalcemia calcium levels before chemotherapy were statistically significantly higher than calcium level after chemotherapy (the Paired t Test P=0.003).

The occurrence of hypercalcemia in patients with solid cancer is a well established phenomenon. Ours is the first study with sufficient sample size to evaluates the impact of different chemotherapy types and doses on calcium level in breast and lung cancer patients with LOH, HHM, and bone metastases. The National Cancer Institute at the National Institute of Health (2010) studied the impact of hypercalcemia treatments such as bisphosphonates, calcitonin, dialysis and others in cancer patients. The impact of chemotherapy drugs or regimens on hypercalcemia has only being described for cisplatin effect in treatment of hypercalcemia has been explored and clarified (National Cancer Institute NCI., 2010).

The main weakness of our study is the lack of PTHrP data, as it is not routinely performed in the general hospital in Penang. However our study was able to gather data on calcium level, before and during chemotherapy, as well as tumor size, presence of metastases.

A case report by Ünal et al. (2008) in Turkey, described how chemotherapy and methylprednisolone affected calcium levels. A three year old child with ALL, presenting with vomiting, fatigue, anorexia and weight loss had calcium level of 19 mg/dl at hospital admission. This child was treated by methylprednisolone, pamidronate, furosemide and normal saline, and chemotherapy with vincristine (1.5mg/m2) and daunomycin (25 mg/m2). After fifteen hours of chemotherapy, calcium levels decreased from 17.1 mg/dL to 12.7 mg/dL, and after 24th hours of chemotherapy calcium levels were reduced to 8.94 mg/dL (Ünal et al., 2008). In another case report Hartley et al. (2012) of 63 years old man diagnosed with squamous cell cancer, hypertension, diabetes and hypercalcemia. His calcium level was 15.5 mg/dL, creatinine level 1.2 mg/dL, albumin level 4.3 mg/dL, and phosphorous level 2.9 mg/dL. The patient was treated for hypercalcemia with intravenous fluid, furosemide and bisphosphonates (Hartley et al., 2012).

Another retrospective study done by He et al. (2008) in Brookdale hospital medical center/Brooklyn/USA, reviewed data for 273 cancer patients (mean age: 63.7 years) with a cancer diagnosis admitted to the hospital between July 2005 to December 2007. This study evaluates the presence and severity of hypercalcemia and response to treatment. Forty one patients (15%) had hypercalcemia (calcium level > 10 gm/dL), 23 (56%) mild hypercalcemia (10-12 mg/dL), 11 (26.8%) moderate hypercalcemia (12-14 mg/dL), and 7 (17.1%) severe hypercalcemia. Sixteen (39%) of the total 273 patients adenocarcinoma, 8 (19.5%) squamous cell carcinoma, 8 (19.5%) multiple myeloma, 3 (7.3%) bladder carcinoma, 3 (7.3%) lymphoma, 1 (2.4%) papillary thyroid carcinoma, 1 (2.4%) CLL and 1 (2.4%) trophoblastic tumor. The main conclusion for this study was that chemotherapy was effective in treatment of severe hypercalcemia of malignancy (i.e., calcium level > 14 gm/dL), as it was effective in managing the tumors. The main differences between this study and ours are that our study specify the types and doses of chemotherapy and the effect in different degrees of hypercalcemia (mild, moderate and severe) (He et al., 2008).

Hartley et al. (2012) described a case report of a 63 years old man diagnosed with squamous cell cancer, hypertension, diabetes and hypercalcemia. His calcium level was 15.5 mg/dL, creatinine level 1.2 mg/dL, albumin level 4.3 gm/dL, and phosphorous level 2.9 mg/dL. The patients were treated for hypercalcemia with intravenous fluid, furosemide and bisphosphonates (Hartley et al., 2012).

The probable mechanism by which calcium level decrease after chemotherapy is by a decrease in PTHrP levels. PTHrP levels have been reported to be increased in 33-84% of breast cancer and 46-47% of lung cancers (Clines, 2011). In a prospective study, Henderson et al. (2006) studied 526 breast cancer patients whose PTHrP level was monitored for 10 years by using immunohistology (Henderson et al., 2006).

Solid cancers at early stages were found to be PTHrP positive. While solid cancers with bone or other organs metastases were found to have negative PTHrP secretion, which led the authors to conclude that breast cancer patient who had a positive PTHrP production were characterized by non invasive phenotype. The study by Henderson et al. (2006) antagonized the old hypothesis that PTHrP found with primary breast cancer stages will increases the likelihood of development of skeletal metastases. PTHrP is the main factor in incidence and/or severity of hypercalcemia (Henderson et al., 2006).

The production of PTHrP is increased with increased of cell proliferation, differentiation, and cancer growth. PTHrP concentration elevated before calcium levels start to increase (Oda et al., 1998; Tovar Sepulveda et al., 2002). Chemotherapeutics drugs attack all the rapidly dividing cells leading to preventing of their proliferating and differentiating by targeting either their DNA or mitosis process (Kelland, 2005; Medicine net. Com., 2010). Hence decreased cell proliferation by chemotherapy will caused reduced PTHrP and therefore reduced hypercalcemia. In previous study among patients with HHM, use of chemotherapy plus anti hypercalcemia treatment resulted suppression of PTHrP levels after 3 to 6 months of treatment, resulting in normal calcium levels (Kanbay et al., 2009).

For those patients who suffer from hypercalcemia in general hospital of Penang the majority of them were treated with pamidronate plus normal saline (n=135; 46.2%) followed by those who received zoledronic acid plus normal saline plus furosemide (n=57; 19.5%) and then followed by those who received only normal saline (n=39; 13.4%). A smaller proportion of the patients were with the combination of pamidronate plus normal saline plus furosemide (n=33; 11.3%) and the least were those treated with zoledronic acid plus normal saline plus furosemide (n=28; 9.6%).

The administration of zoledronic acid to malignant hypercalcemic mice would lead to a decreased in osteoclast cell i.e., increased in bone density and decreased in hypercalcemia, but not decrease in PTHrP production by tumor cells, and have no impact on tumor cell proliferation (Tannehill-gregg, 2006). Thus, reduction of PTHrP level associated with the use of chemotherapy and bisphosphonates (such as pamidronate or zoledronic acid) combination is mainly caused by the chemotherapy itself rather than by bisphosphonates, since chemotherapy caused the changes in the cancer cell proliferation. So this can confirm the results of our study which show strong association between chemotherapy type with onset and severity of hypercalcemia and chemotherapy could be considered as a very potent treatment for hypercalcemia.

In conclusion

In our study cohort we found that chemotherapy plays an important role in the treatment of hypercalcemia i.e., reducing its onset and severity most probably through reducing PTHrP level.

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