

A retrospective analysis of the factors associated with hypercalcaemia in patients with advanced cancer

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Hypercalcaemia, a common complication of advanced cancer, causes multiple clinical symptoms, deteriorates patients' quality of life, and is associated with poor prognoses. This study aimed to identify the factors that may be associated with hypercalcaemia in advanced cancer by retrospectively reviewing the medical records of patients ($n = 404$) admitted to the palliative ward of the Kaohsiung Medical University Hospital, Taiwan, from 2006 to 2008. Patients' demographics, clinical data and symptoms were recorded. Seventy-nine of 404 patients had hypercalcaemia (19.6%), predominant in cases of head-and-neck cancer and haematological malignancies ($P < 0.05$), but not in those of bone metastases. Hypercalcaemia was associated with consciousness disturbances and leucocytosis ($P < 0.05$). We recommend that ionised (corrected) calcium levels be monitored clinically in patients with advanced cancer especially when consciousness disturbances are noted, or when head-and-neck or haematological malignancies are present. Testing of free calcium levels is also recommended in patients with leucocytosis.

Keywords: hypercalcaemia, advanced cancer, head-and-neck cancer, leucocytosis.

INTRODUCTION

Hypercalcaemia is a common complication of advanced cancer (Muggia 1990; Theriault 1993; Stewart 2005) such that up to 30% of patients with advanced cancer are diagnosed with hypercalcaemia (Lamy *et al.* 2001; Stewart 2005; Shibata 2008; Chapireau *et al.* 2010). Hypercalcaemia leads to poor prognoses and is often life-threatening.

Survival times range from 1 to 6 months in hypercalcaemic cancer patients (Ralston *et al.* 1990; Penel *et al.* 2005; Alsirafy *et al.* 2009). It has been reported that patients with breast cancer, multiple myeloma, lymphoma, and lung cancer are likely to develop hypercalcaemia (Burt & Brennan 1980; Muggia 1990).

Hypercalcaemia-associated clinical symptoms include polyuria, polydipsia, dehydration, anorexia, nausea, constipation, weakness, confusion and delirium (Ralston *et al.* 1990; Lamy *et al.* 2001; Iwase *et al.* 2003; Inzucchi 2004). The higher the serum levels of ionised (corrected) calcium, the more intense the symptoms (Inzucchi 2004; Bradley & Hoskin 2006). These symptoms lead to poor quality of life in patients with advanced cancer. Management of hypercalcaemia, especially with bisphosphonate administration, can relieve patients' symptoms and

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improve their quality of life (Ralston *et al.* 1990; Lamy *et al.* 2001; Saunders *et al.* 2004).

Paraneoplastic syndrome is a disease manifesting with a collection of symptoms that result from the presence of cancer(s) in some patients and leads to high morbidity and possibly mortality. Among paraneoplastic syndromes, hypercalcaemia-leucocytosis syndrome occurs less frequently than hypercalcaemia or leucocytosis alone, and if present, confers poor prognosis (Yoneda *et al.* 1991; Hiraki *et al.* 2004; Chapireau *et al.* 2010). However, the relationship between advanced cancer and paraneoplastic syndrome has not been well-studied. Therefore, we investigated the prevalence of hypercalcaemia in patients with advanced cancer and assessed associated clinical conditions, which may cause poor quality of life. The treatment strategy is to detect and manage hypercalcaemia as early as possible and to provide high-quality care for patients with advanced cancer.

PATIENTS AND METHODS

Patients and data collection

We reviewed retrospectively the medical records of patients with advanced cancer admitted to the palliative-care ward of the Kaohsiung Medical University Hospital, Taiwan, from January 2006 to December 2008. Our study was approved by our institutional review board. Age, sex, primary cancer diagnosis and metastatic conditions diagnosed by computed tomography, bone scan, sonography and magnetic resonance imaging, were documented. Paraneoplastic symptoms, including lethargy, anorexia, abdominal fullness, oedema, infection, breakthrough pain, ascites, consciousness disturbances (or unconsciousness), fungating tumour wounds, fever, bleeding, severe cough, insomnia and dizziness, were documented. The laboratory data at patient admittance included white blood cell counts, platelet counts, C-reactive protein, haemoglobin, aspartate transaminase, alanine transaminase, creatinine, sodium, potassium, ammonia, ionised (corrected) calcium, prothrombin time (normalised international ratio) and albumin.

Patients' grouping

Patients were classified into two groups according to presence or absence of hypercalcaemia. We used an ionised (corrected) calcium level of >5.5 mg/dL to indicate hypercalcaemia according to laboratory criteria (4.0–5.5 mg/dL or 1.0–1.3 mmol/L) established in the Kaohsiung Medical University Hospital. Ionised (corrected) calcium better

represents functional calcium levels *in vivo* than does total serum calcium (Saunders *et al.* 2004).

Statistical analysis

Descriptive analyses were used to assess the differences between the demographic characteristics, paraneoplastic symptoms and blood parameters in the hypercalcaemic or non-hypercalcaemic group. Logistic regression analysis was used to assess associations between the clinical factors and hypercalcaemia. We used 14 variables, which differed significantly by the univariate analyses for the full analysis. Subsequently, a stepwise method was used to reduce the number of variables. Finally, in addition to the stepwise model, we included age, sex and bone metastases to perform our final analysis. The SPSS statistical package was used. A *P*-value of <0.05 indicated statistical significance.

RESULTS

Of the 404 patients, 79 (19.6%) had hypercalcaemia. Demographic characteristics of the two patient groups are shown in Table 1. The difference in average patient age between the two groups was not statistically significant (61.9 ± 13.1 and 58.9 ± 13.4 years respectively). Further, 41.5% and 26.6% of patients were female in the non-hypercalcaemic and hypercalcaemic groups respectively.

The primary cancer diagnoses of terminal cancer patients are shown in Table 1. The prevalence of head-and-neck cancer and haematology malignancy cases were significantly different between the two groups. Head-and-neck cancers predominated in the hypercalcaemic group ($P < 0.001$). The two groups had similar metastatic conditions; however, the number of bone and brain metastases were higher in the non-hypercalcaemic group than in the hypercalcaemic group ($P < 0.05$).

Paraneoplastic symptoms in the terminal patients are presented in Table 2. Most of the symptoms were not significantly different between the two groups. Abdominal fullness occurred more frequently in the non-hypercalcaemic group ($P < 0.05$). In contrast, the proportion of cases with consciousness disturbances (or unconsciousness) and fungating tumour wounds were significantly higher in the hypercalcaemic group ($P < 0.05$).

Patients' laboratory results were mostly similar between the two groups (Table 3). However, alanine transaminase was higher in the non-hypercalcaemic group ($P = 0.021$), whereas white blood cell counts and haemoglobin were significantly higher in the hypercalcaemic group ($P < 0.001$).

Table 1. Comparison of age, sex, cancer types, metastatic sites and performance status between the hypercalcaemic and non-hypercalcaemic groups (demographics of study subjects)

	Non-hypercalcaemia (<i>n</i> = 325)	Hypercalcaemia† (<i>n</i> = 79)	<i>P</i> -value*
Age (mean ± SD)	61.9 ± 13.1	58.9 ± 13.4	0.776
Female	135 (41.5%)	21 (26.6%)	0.002
Male	190 (58.5%)	58 (73.4%)	
Primary cancer diagnosis			
Head and neck	56 (17.2%)	34 (43.0%)	<0.001
Pancreatic cancer	14 (4.3%)	0 (0%)	0.082
Breast cancer	22 (6.8%)	2 (2.5%)	0.191
Gastrointestinal tract	65 (20.0%)	17 (21.5%)	0.757
Lung and respiratory	60 (18.5%)	8 (10.1%)	0.093
Hepatobiliary	46 (14.2%)	10 (12.7%)	0.857
Urinary tract	18 (5.5%)	0 (0%)	0.03
Gynaecological	24 (7.4%)	0 (0%)	0.007
Haematology	8 (2.5%)	6 (7.6%)	0.037
Other	12 (3.7%)	2 (2.5%)	0.99
Metastasis			
Local invasion	85 (26.2%)	27 (34.2%)	0.098
Lung	73 (22.5%)	20 (25.3%)	0.655
Liver	84 (25.8%)	22 (27.8%)	0.776
Bone	107 (32.9%)	14 (17.7%)	0.009
Brain	56 (17.2%)	6 (7.6%)	0.036

**T*-test or chi-squared test.

†Ionised (corrected) calcium > 5.5 mg/dL (1.3 mmol/L).

Table 2. Comparison of cancer-related symptoms in terminal patients between the hypercalcaemic and non-hypercalcaemic groups (comparison of terminal cancer symptoms among different age groups)

	Non-hypercalcaemia (<i>n</i> = 325)	Hypercalcaemia† (<i>n</i> = 79)	<i>P</i> -value*
Lethargy	321 (98.8%)	79 (100%)	0.99
Anorexia	267 (82.2%)	63 (79.7%)	0.628
Abdominal fullness	144 (44.3%)	18 (22.8%)	<0.001
Oedema	85 (26.2%)	15 (19.0%)	0.244
Infection	58 (17.8%)	22 (27.8%)	0.058
Breakthrough pain	53 (16.3%)	13 (16.5%)	0.99
Ascites	40 (12.3%)	6 (7.6%)	0.323
Consciousness disturbance or unconsciousness	36 (11.1%)	18 (22.8%)	0.009
Fungating tumour wound	28 (8.6%)	18 (22.8%)	0.001
Fever	38 (11.7%)	6 (7.6%)	0.420
Bleeding	40 (12.3%)	6 (7.6%)	0.323
Severe cough	24 (7.4%)	8 (10.1%)	0.485
Insomnia	22 (6.8%)	2 (2.5%)	0.191
Dizziness	4 (1.2%)	2 (2.5%)	0.334

*Chi-squared test.

†Ionised (corrected) calcium > 5.5 mg/dL (1.3 mmol/L).

The logistic regression results assessing associating factors in the hypercalcaemic patients are presented in Table 4. White blood cell counts were associated with hypercalcaemia (OR: 1.04, 95% CI: 1.00–1.08), while consciousness disturbances (or unconsciousness) were most closely associated with hypercalcaemia (OR: 2.78, 95% CI: 1.38–5.59). Head-and-neck cancer and haematology malignancies were associated with hypercalcaemia (OR: 3.02, 95% CI: 1.51–6.03; OR: 7.71, 95% CI: 2.27–26.20). Age, sex, bone and brain metastases, infection,

fungating tumour wounds, abdominal fullness, alanine transaminase and albumin were not associated with hypercalcaemia.

DISCUSSION

In the past, malignancy-associated hypercalcaemia was determined generally by measuring the total serum calcium levels. However, this method requires correction for serum albumin (Ralston *et al.* 1990; Lamy *et al.* 2001;

Table 3. Comparison of blood parameters between the hypercalcaemic and non-hypercalcaemic groups presented as mean (standard deviation)

	Non-hypercalcaemia (<i>n</i> = 431)		Hypercalcaemia† (<i>n</i> = 97)		<i>P</i> -value*
WBC (10 ³ /μL)	12.1	(6.5)	15.8	(10.0)	<0.001
PLT (10 ³ /μL)	282.6	(149.3)	278.8	(147.1)	0.461
HGB (g/dL)	9.6	(2.1)	9.9	(2.4)	0.029
CRP (mg/L)	110.1	(79.0)	141.7	(86.6)	0.253
AST (IU/L)	63.4	(62.3)	59.9	(65.6)	0.388
ALT (IU/L)	55.3	(86.6)	40.0	(35.7)	0.021
CREA (mg/dL)	1.2	(1.6)	1.3	(1.2)	0.420
Na (mmol/L)	133.0	(5.9)	136.0	(7.9)	0.184
K (mmol/L)	4.2	(0.8)	4.1	(0.8)	0.619
Ammonia (μg/dL)	89.8	(54.4)	92.3	(59.0)	0.537
PT-INR	1.3	(0.6)	1.3	(0.3)	0.769
Albumin (g/dL)	2.8	(0.6)	2.7	(0.4)	0.024
iCa (mg/dL)	4.8	(0.4)	6.9	(1.2)	<0.001

**T*-test.

†Ionised (corrected) calcium > 5.5 mg/dL (1.3 mmol/L).

WBC, white blood cell counts; PLT, platelets; HGB, haemoglobin; CRP, C-reactive protein; AST, aspartate transaminase; ALT, alanine transaminase; CREA, creatinine; Na, sodium; K, potassium; PT-INR, prothrombin time (international ratio), iCa, ionised calcium.

Table 4. Associated factors with hypercalcaemia by logistic regression analysis

Factors	Odds ratio (95.0% confidence interval)		
	Full model	Stepwise model	Final model
Age	0.986 (0.957–1.015)	–	0.988 (0.965–1.011)
Gender (female vs. male)	0.918 (0.413–2.040)	–	1.094 (0.578–2.067)
Head and neck cancers	1.944 (0.744–5.081)	3.339 (1.621–6.877)**	3.019 (1.511–6.030)**
Urinary tract cancers	0†	0†	–
Gynaecological cancers	0†	0†	–
Haematology malignant	10.304 (2.180–43.703)**	11.948 (3.100–46.042)**	7.710 (2.268–26.205)**
Bone metastasis	0.738 (0.320–1.703)	–	0.776 (0.384–1.570)
Brain metastasis	0.411 (0.138–1.223)	–	–
Infection	1.852 (0.824–4.162)	–	–
Consciousness disturbance or unconsciousness	3.186 (1.285–7.896)*	3.671 (1.534–8.766)**	2.779 (1.383–5.585)**
Fungating tumour wound	2.270 (0.753–6.841)	–	–
Abdominal fullness	0.572 (0.269–1.217)	–	–
WBC (10 ³ /μL)	1.034 (0.991–1.079)	1.042 (1.001–1.084)*	1.044 (1.009–1.080)*
HGB (g/dL)	1.214 (1.030–1.432)*	1.178 (1.013–1.370)*	1.140 (1.003–1.296)*
ALT (IU/L)	0.998 (0.991–1.005)	–	–
Albumin (g/dL)	0.952 (0.451–2.007)	–	–

***P* < 0.01, **P* < 0.05.

†Patients with these cancer types did not suffer from hypercalcaemia, odds ratio could not be calculated.

WBC, white blood cell counts; HGB, haemoglobin; ALT, alanine transaminase.

Iwase *et al.* 2003; Penel *et al.* 2005; Alsirafy *et al.* 2009) because patients with malignancies also develop hypoalbuminaemia. Therefore, total calcium levels are poor representatives of hypercalcaemia (Saunders *et al.* 2004). We used serum ionised (corrected) calcium because it accurately reflects patients' active calcium levels and does not require adjusting for albumin. Measuring ionised (corrected) calcium, but not total serum calcium, is therefore indicated in patients with advanced cancer.

In our study, hypercalcaemia was found to be associated with head-and-neck cancers in patients with advanced cancer, which concurred with a previous report by Alsirafy *et al.* (2009) who found high hypercalcaemia

prevalence (51.1%) in patients with advanced head-and-neck cancer. In these patients, low incidence of hypercalcaemia had been noted in the early disease stages, but ionised (corrected) calcium levels was found to rise in advanced disease stages (Bradley & Hoskin 2006). The occurrence of head-and-neck cancers is associated with chronic carcinogen intake, especially tobacco smoking and alcohol consumption (Freedman *et al.* 2007; Hashibe *et al.* 2013), which are typical male behaviours in Taiwan (Wen *et al.* 2005; Wu *et al.* 2006). Male sex predominated in the hypercalcaemia group, in which head-and-neck cancer (43%) was the major malignancy in our study. However, there was no strong association between male

sex and hypercalcaemia after adjustment for potential confounding factors by logistic regression.

Hypercalcaemia also occurred significantly frequently in patients with haematological malignancies, a finding that corroborates those of a study by Sargent and Smith (2010). Hypercalcaemia associated with haematological malignancies is likely driven by parathyroid hormone-related protein (PTHrP) (Firkin *et al.* 1998). In our study, bone metastasis was not highly associated with hypercalcaemia; whereas, previous studies have demonstrated that the incidence of bone metastasis in hypercalcaemic patients is >60% (Ralston *et al.* 1990; Lamy *et al.* 2001). However, Kovacs *et al.* established that local osteolytic factors surrounding the bone metastases were not the major cause of malignant hypercalcaemia in the patients receiving palliative care (Kovacs *et al.* 1995).

Overall, 4 potential underlying mechanisms leading to hypercalcaemia have been reported previously in patients with advanced cancer (Stewart 2005). Humoral hypercalcaemia is thought to be the major mechanism underlying the prevalence of hypercalcaemia in malignancy (Stewart 2005). Accordingly, Alsirafy *et al.* hypothesised that humoral hypercalcaemia was likely the primary mechanism in patients with head-and-neck cancer (Alsirafy *et al.* 2009). Our study shows a similar trend to that reported by Alsirafy *et al.* Humoral hypercalcaemia is mediated by PTHrP frequently released by squamous cell carcinomas (Broadus *et al.* 1988).

The second potential mechanism is the bone tissue resorption mediated by osteolytic metastases (Mundy 2002; Roodman 2004), which were discussed above. The third cause is increased production of 1,25-dihydroxyvitamin D by malignant cells (Seymour & Gagel 1993; Roodman 1997). The last and the least commonly observed cause of hypercalcaemia is ectopic parathyroid hormone secretion by some malignant tumours (Stewart 2005). The cross-sectional study design of our research did not allow for clarification of the potential aetiological factors involved in our hypercalcaemia subjects. Therefore, further research to determine the aetiology of hypercalcaemia in patients with advanced cancer is warranted.

By logistic regression analysis, the consciousness disturbances (or unconsciousness) were found to be positively associated with hypercalcaemia. To the best of our knowledge, there were few reports to describe such a relationship, which is only one of the clinical symptoms in patients with advanced cancer. According to the literature, hypercalcaemia results in consciousness disturbances (Ralston *et al.* 1990; Lamy *et al.* 2001; Inzucchi 2004), which influence the quality of life in patients with advanced cancer, cause distress to family members and caregivers,

and pose management challenges to healthcare providers (Delgado-Guay *et al.* 2008; Bruera *et al.* 2009). Occurrence of consciousness disturbances potentially harbinger the occurrence of hypercalcaemia in a palliative setting. Thus, medical practitioners should be quick to manage electrolyte disturbances as to relieve patients' and carers' suffering. Accordingly, management of hypercalcaemia would improve clinical symptoms.

White blood cell counts were statistically correlated to hypercalcaemia in our study. Among cases of paraneoplastic syndromes associated with various cancers, hypercalcaemia and leucocytosis are the two most common symptoms (Yoneda *et al.* 1991). A relationship between hypercalcaemia and leucocytosis was reported in patients with lung and oral cancer previously (Yoneda *et al.* 1991; Hiraki *et al.* 2004). It was proposed that a common mechanism likely underlies hypercalcaemia and leucocytosis. This was found to be mediated by stimulation via humoral factors produced by cancer cells, such as granulocyte colony-stimulating factor (G-CSF) or PTHrP (Yoneda *et al.* 1991; Hiraki *et al.* 2004; Chapireau *et al.* 2010). Our results supported the association between hypercalcaemia and leucocytosis.

In our study, the prevalence of hypercalcaemia was high (19.6%) in patients with advanced cancer, especially in those with head-and-neck cancer (43.0%). At the same time, our study supported previous reports showing that hypercalcaemia was significantly correlated with leucocytosis. The goal of palliative care is to improve the quality of life for patients with advanced cancer. Thus, we suggest that medical practitioners in palliative wards monitor ionised (corrected) calcium levels in patients with head-and-neck cancer and haematological malignancies. Because hypercalcaemia prevalence could be as high as 20 to 30%, it would likely lead to consciousness loss or confusion, making caregiving more difficult. Furthermore, our study found that hypercalcaemia was probably one of the mechanisms underlying consciousness disturbances or unconsciousness in patients with advanced cancer. Thus, careful attention should be paid to electrolytes, especially ionised (corrected) calcium, in these patients (Stewart 2005).

Our study was limited in two different aspects. We did not check G-CSF or PTHrP levels in the patients; this represents 1 study limitation. Furthermore, the retrospective design of our study could not allow investigation of the relationship between factors underlying hypercalcaemia and leucocytosis, and various cancers. Further research is needed to explore the mechanisms underlying hypercalcaemia and leucocytosis more fully in patients with advanced cancer.

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Conflict of interest statement

The authors declare no conflict of interest.

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