Original Article

Prognostic Factors of Hypercalcemia of Malignancy

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Objective: Hypercalcemia of malignancy [HCM] relates to advanced stage of cancer and associates with short survival time. However, the prognostic factors of HCM are limited to determine. The aim of the present study is to evaluate clinical outcomes and prognostic factors of hypercalcemia of malignancy.

Materials and Methods: A retrospective study was designed and 81 of patients with newly diagnosed HCM in Srinagarind University Hospital were enrolled during January 2006 to 2010. Clinical data and clinical outcomes were evaluated by uni- and multivariate analysis.

Results: The majority of patients were male (60.4%). The average age of patients was 56 years old. The most common cause of HCM was lung cancer (62.9%) followed by hematologic cancer (26.9%), urothelial cancer (11.1%), gastro-intestinal cancer (4.49%), and breast cancer (4.49%). The most common presenting symptom of HCM was neuromuscular symptoms. The months (95% confidence interval [CI]: 0.76 to 3.43). Patients with age less than 40 year-old and receiving treatment with corticosteroid were a significant factor in univariate analysis. Only the factor of receiving treatment with corticosteroid was a good significant prognostic factor (hazard ratio was 0.86; 95% CI: 0.81 to 0.99).

Conclusion: HCM is a disease with high mortality rate. HCM Patients, especially hematologic malignancy with corticosteroid treatment, possibly had good prognosis compared to other groups.

Keywords: Hypercalcemia, Cancer, Hypercalcemia of malignancy, HCM

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Hypercalcemia is a common metabolic disorder in oncologic emergencies[1]. Hypercalcemia of malignancy [HCM] was found 20 to 30% of all cancer patients[2]. It associatesd with advanced stage of cancer and relatesd to poor prognosis. Patients who had HCM always relatedd to high mortality or death within 30 days[1,3]. There isare previous studies, which studied the cause of hypercalcemia in patients admitted in the hospital, and the results revealed that cancer is the most common cause of hypercalcemia. In addition, lung cancer had the highest incidence causing hypercalcemia followed by cancer of GI tract, cancer of KUB and reproductive system, hematologic malignancy, cancer of head and neck region, cancer of unknown origin, breast cancer and skin cancer, respectively[4,5].

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Clinical manifestation of HCM has multiplicity such as fatigue, anorexia, constipation, and confusion. These symptoms relate to the severity of HCM more than the levels of calcium in serum. Untreated patients with high levels of hypercalcemia may cause death, therefore, clinical improvement and better quality of life may be occurred after patients receiving effective treatment[6,7]. Common clinical presentation according to organ system areare kidney system: polyuria, polydipsia, and arrhythmia; gastrointestinal system: loss of appetite, nausea, vomiting, weight loss, and constipation; nervous system: weakness, tiredness, loss of initiative, depression, dizziness, and loss of appetite; musculoskeletal system: muscle weakness, weakened reflexes, and osteoporosis; and cardio-vascular system: arrhythmia and hypertension[8,9].

Treatment of HCM is determined by clinical presentation and levels of calcium. Patients will receive treatment when the asymptomatic patients who had levels of calcium more than 14 mg/dL or symptomatic patients with levels of calcium is more than 12 mg/dL.

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The treatment of HCM includes intravenous hydration with normal saline, intravenous furosemide, intravenous bisphosphonate which acts as bone resorption blockage, calcitonin, glucocorticoids, and dialysis[10,11]. There are only few previous reports, which studied about HCM especially determining thee prognostic factors in HCM[12-14]. Thus, the present study aims to evaluate clinical outcome in ·Srinagarind University Hospital and to identify the prognostic factors of HCM.

Materials and Methods

A retrospective study was conducted in HCM patients, who received treatment in Srinagarind Hospital, Khon Kaen University (a 1,000-bed university hospital), Khon Kaen, Thailand, during January 2006 to December 2010. The study was reviewed and approved by the institutional review board (HE 561260).

HCM was defined as patients who were diagnosed as malignancy and had serum calcium levels more than 10.8 mg/dL. Patients with age more than 15 years newly diagnosed as HCM and available medical records were enrolled in the present study.

Demographic data including sex, age, types of cancer, clinical symptoms of first presentation, levels of corrected calcium, renal function status, and treatment modalities were recorded. The treatment modalities were intravenous hydration, furosemide, intravenous bisphosphonate, glucocorticosteroid, and dialysis.

Statistical considerations

The objective of the present study is to determine clinical outcomes and prognostic factors of HCM patients. The survival time was defined as the period since the date of HCM diagnosis to the date of death from any causes. Patients' characteristics and cancer data were summarized as mean and percentage. The cumulative survival rates were calculated using the Kaplan-Meier method and the log-rank test were used to calculate the difference among. Variable factors were analyzed for prognostic factors including sex, age, types of cancer, clinical symptoms of the first presentation, levels of corrected calcium, renal function status, and treatment modalities. Univariate analysis was performed using the Chi-squared test. Multivariate analysis was performed with the Cox proportional hazard model. The chance of achieving overall statistically significant results was concerned when the *p*-value is less than 0.05 and 95% confidence interval [CI] was also used. The statistical analysis was performed by using Stata software version 11. The data was closed for analysis in August 2014.

Results

Demographic data and clinical presentation

The present study included 81 of HCM patients in total. The patients' characteristics are presented in Table 1. There was higher proportion of male participants. The age group of HCM patients with the highest incidence was 41 to 60 years old.

The most common cause of HCM was lung

Table 1. Baseline characteristics of the 81 patients

Variable	n (%)
Sex	
Male	49 (60.4)
Female	32 (39.5)
Age	
≤21 year	1 (1.2)
21 to 40 year	7 (8.6)
41 to 60 year	43 (53.0)
>60 year	30 (37.0)
Hypercalcemia	
Calcium (mg/dL) (range)	13.5 (9.4 to 19.5)
Level of Albumin	
≤3.5 mg/dl	56 (69.1)
>3.5 mg/dl	25 (30.8)
Level of Cr	
≤1.5 mg/dl	49 (60.4)
1.6 to 3 mg/dl	22 (27.1)
>3 mg/dl	10 (12.3)
Clinical presentation	
Neuromusscular	50 (61.7)
Gastroentestinal	14 (17.2)
Renal	9 (11.1)
Cardiac	1 (1.2)
Back pain	1 (1.2)
Malignancy	
Lung	51(62.9)
Hematologic	24 (29.6)
Urogenital	9 (11.1)
Gastro-intestinal	4 (4.9)
Breast	4 (4.9)
Head and neck	3 (3.7)
Skin	3 (3.7)
Unknown primary	7 (8.6)
Treatment	
Intravenous hydration	82 (100)
Furosemide	49 (59.8)
Bisphosphanate	37 (45.1)
Glucocorticosteroid	19 (23.2)
Dialysis	5 (6.1)

cancer (26.9%) followed by hematologic cancer (29.6%), urothelial cancer (11.1%), gastro-intestinal cancer (4.49%), and breast cancer (4.49%)-average level of corrected calcium in HCM patients was 14 mg/dL.

The common presenting symptoms were neuromuscular symptoms (61.7%), gastrointestinal symptoms (17.24%), renal symptom (11.11%), low back pain (3.36%), and cardiac symptom (1.23%). All HCM patients received intravenous hydration. In addition, a majority of patients also received intravenous furosemide, intravenous bisphosphonate, corticosteroid, and dialysis. The most patients who received corticosteroid treatment were hematologic malignancy patients (84.2%).

Prognostic factors of HCM patients

The median overall survival time of all HCM patients was 2.1 months (95% CI, range 0.76 to 3.43 months) (Figure 1). Six-months and 1-year survival rate were 45.0% and 22.19%, respectively. Both univariate and multivariate analysis showed that patients who received treatment with intravenous corticosteroid significantly associated with longer overall survival time compared to another age group Table 2). Age more than 40 years old was a significant prognostic factor ~~in~~analyzed by the univariate analysis, but this factor was not statistically significant~~ce~~ in multivariate analysis. Sex, types of cancer, clinical symptoms of the first presentation, levels of corrected calcium, levels of creatinine, levels of albumin, intravenous furosemide, intravenous bisphosphonate, and dialysis were not significant prognostic factors.

Discussion

Hypercalcemia is a serious condition leading to high rate of mortality in patients with malignancy. Malignant patients, which were commonly found hypercalcemia, ~~was~~were lung cancer, multiple myeloma, lymphoma, and urothelial cancer. These findings were fairly consistent with previous reports[4,5].

HCM was commonly occurred in patients at the age of 41 to 60 years because cancers are usually developed in patients during this age group[15-17]. Therefore, these patients generally have complications from cancer including hypercalcemia.

The most common clinical presentation of HCM patients was neuromuscular symptoms. Normally, patients will be brought to the hospital when the symptoms are severe. Patients with serious complication such as alteration of conscious, which are the most leading cause that brings patients to the hospital, are finally brought to the hospital because it is fatal alarm feature, which is easily detected by patients' relatives.

The present study presented that median overall survival time of HCM patients was 2.1 months. The previous reports showed that median overall

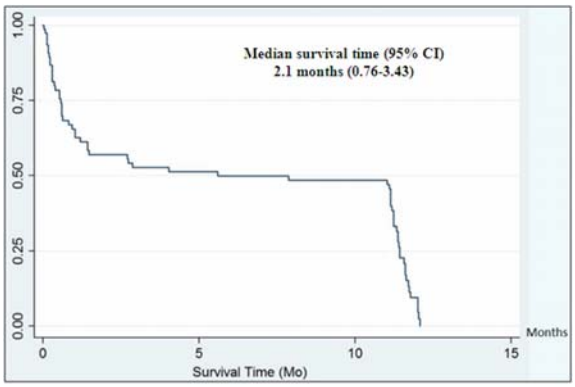

Figure 1. Kaplan-Meier survival curve used to analyze the overall survival time of 81 hypercalcemia of malignancy.

Table 2. Prognostic factors of 81 hypercalcemia of malignant patients

Variable	Univariate			Multivariate		
	Median survival time (months)	95% confidence interval	*p*-value	HR	95% CI	*p*-value
Age (years)			0.05	0.79	0.38 to 1.12	0.180
≤40	18.04	7.527 to 43.847				
>40	1.77	0.901 to 1.098				
Corticosteroid			0.058	0.86	0.81 to 0.99	0.04
Yes	3.02	0.116 to 5.883				
No	1.94	0.900 to 1.099				

survival time was 3 months. This possibly indicates that cancer patients with HCM could present with nonspecific symptoms. In addition, cancers that commonly cause HCM in the present study were lung cancer, hematologic cancer, and urothelial cancer. Theses malignancies were aggressive and had shorter survival time compared with breast cancer, which was found that it was the common cause of HCM in other previous reports[5]. Consequently, it is difficult to make a definite diagnosis of HCM leading to delayed diagnosis and delayed specific treatment. This can seriously affect the treatment outcome and prognosis of patients.

The results of the present study presented that treatment with corticosteroid is a good prognostic factor because the majority of patients who received corticosteroid treatment were hematologic malignancy, which had good response of treatment. Consequently, these patients had longer survival time compared another group.

The present study has limitation. The present study because it is a retrospective study and the clinical data recorded especially the performance status of patients, which significantly relates to the prognosis of patients, were not perfectly complete especially because all necessary clinical data were not completely recorded at the beginning period of time when of cancer registration system was established.

Patients with younger age (less than 40 years) were associated with longer survival times compared to the older age patients in univariate analysis. The-ese are possibly because younger age patients may have better performance status than older age group. Previous studies established that performance status of HCM patients is a prognostic factor in many cancers[12,14]. Other factors including serum albumin, renal function status, and types of treatment did not significantly indicate prognos-is in the preseny study. This is, probable due to the fact that too small sample size was included. Previous reports revealed that high level of serum corrected calcium, low level of albuminemia, squamous cell carcinoma, bone metastasis, and liver metastasis were significant prognostic factors[12].

In subset analysis, the present study showed that levels of calcemia >2.83 mmol/l (RR 5.07), hypoalbuminemia (RR 7.42), liver metastasis (RR 4.34), and squamous cell carcinomas (RR 2.21) were independent factors in patients with survival time less than 60 days.

The present study has limitation because it is a retrospective study and the clinical data recorded especially the performance status of patients, which significantly relates to the prognosis of patients, were not perfectly complete because all necessary clinical data were not completely recorded at the beginning period of time when cancer registration system was established.

Conclusion

HCM is a disease with high mortality rate. HCM Patients, especially hematologic malignancy with corticosteroid treatment, possibly had good prognosis compared to other groups.

What is already known on this topic?

Hypercalcemia of malignancy [HCM] relates to advanced stage of cancer and associates with short survival time. The most common causes of HCM were lung cancer and hematologic malignancies.

What is this study adds?

The present study showed the most common clinical manifestations of the patients with HCM were neuromuscular symptoms, gastrointestinal symptoms, renal symptom, low back pain, and cardiac symptom, respectively. Unlike some previous studies showed that the common symptoms were gastrointestinal symptoms, renal symptom, and neuromuscular symptoms. There were few studies, which focused on studying the treatment outcome of steroid indicating a good prognostic factor.

Potential conflicts of interest

The authors declare no conflict of interest.

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