

## RESEARCH ARTICLE

# Analysis on Survival and Prognostic Factors for Cancer Patients with Malignancy-associated Hypercalcemia

Su-Jie Zhang<sup>1</sup>, Yi Hu<sup>1\*</sup>, Jing Cao<sup>2</sup>, Hai-Li Qian<sup>3</sup>, Shun-Chang Jiao<sup>1</sup>, Zhe-Feng Liu<sup>1</sup>, Hai-Tao Tao<sup>1</sup>, Lu Han<sup>1</sup>

### Abstract

**Objective:** To explore the incidence, clinical characteristics, diagnosis and treatment strategies, prognosis of patients with malignancy-associated hypercalcemia (MAH). **Methods:** The data of 115 patients with MAH who were treated at the Medical Oncology Department of Chinese PLA General Hospital from Jan., 2001 to Dec., 2010 was retrospectively reviewed. Survival analysis was performed using the Kaplan-Meier method and the Cox proportional hazard model with statistic software SPSS 18.0. **Results:** The patients had blood calcium levels ranging from 2.77 to 4.87 mmol/L. Except for 9 cases who died or were discharged within 5 days after admission, all other patients recovered to normal blood calcium level after treatment with bisphosphonates or intravenous hydration and diuretics; their survival after occurrence of MAH was from 1 day to 4,051 days, and the median survival time was only 50 days. In the log-rank test, the male, renal metastasis, central nervous system symptoms and hypercalcemia occurring over 140 days after cancer diagnosis were predictors of poor survival ( $P=0.002$ ,  $P=0.046$ ,  $P=0.000$ ,  $P=0.009$ ). In the COX analysis, being male, central nervous system symptoms and hypercalcemia lasting over 140 days after cancer diagnosis were independent prognostic factors for survival time (RR=2.131,  $P=0.027$ ; RR=3.054,  $P=0.002$ ; RR=2.403,  $P=0.001$ ). According to these factors, a score system was established to predict the patient prognosis and adjust the treatment. **Conclusion:** Cancer patients with MAH have an extremely poor median survival. Some independent factors indicate poor prognosis, including male gender, central nervous system symptoms and hypercalcemia lasting over 140 days after cancer diagnosis. The prognostic score can serve as a reference for MAH prognosis and treatment, worthy of further investigation.

**Keywords:** Hypercalcemia - cancer - prognostic factor - gender - CNS symptoms

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### Introduction

Malignancy-associated hypercalcemia (MAH), one of the most serious and common complications of malignancy at the advanced stage and with a prevalence around 3%~30% in all cancer patients, is not univocally correlated with the occurrence of bone metastasis (Grill et al., 2000; Stewart et al., 2005). However, the incidence of hypercalcemia in China is far below the number (Xie et al., 2006; Shi et al., 2008). Early and prolonged application of bisphosphonates in cancer patients with bone metastasis has, to some extent, decreased the frequency of MAH. MAH is usually diagnosed in patients with multiple myeloma, lung cancer (especially if squamous-cell histology), breast cancer, head and neck cancer, kidney and urinary tract cancer and prostate cancer. Patients occurring MAH have a poor prognosis, with a median overall survival ranging from 60 to 90 days (Penel et al., 2008).

Due to the severe effects of MAH on patients' quality of life and survival, the data of 115 patients with

hypercalcemia in 8 096 screened cancer patients was retrospectively reviewed, and meanwhile, the incidence, clinical characteristics, diagnosis and treatment and survival prognosis of MAH patients were also analyzed in this study.

### Materials and Methods

#### General data

One hundred and fifteen cancer patients with MAH who were treated at the Medical Oncology Department of Chinese PLA General Hospital from Jan., 2001 to Dec., 2010 were selected. Inclusion criteria: (1) biopsy-proven solid tumors; (2) hypercalcemia defined by serum calcium above 2.75 mmol/L.

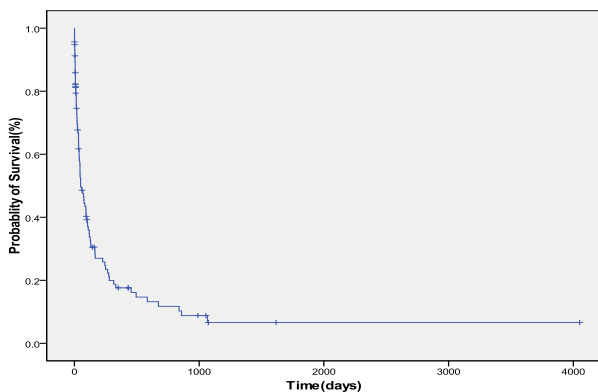
#### Methods

For each patient, we recorded the age, gender, primary site of disease, histological type, presence of visceral metastasis (liver, lung, kidney and brain), bone metastasis, number of metastatic sites, time interval between the

<sup>1</sup>Department of Oncology, Chinese PLA General Hospital, <sup>2</sup>Pharmacy Department, The Second Artillery General Hospital of Chinese People's Liberation Army, <sup>3</sup>National Key Lab of Molecular Oncology, Cancer Institute & Hospital, CAMS, Beijing, China  
\*For correspondence: [huyi040@aliyun.com](mailto:huyi040@aliyun.com)

**Table 1. Primaries and Histological Subtypes**

Primaries	n(%)
Lung	34(29.6%)
Breast	13 (11.3%)
Kidney	9 (7.8%)
Stomach	9 (7.8%)
Liver	8 (7.0%)
Esophagus	7 (6.1%)
Colon	5 (4.3%)
Recta	5 (4.3%)
Uterine cervix	3 (2.6%)
Bladder	3 (2.6%)
Prostate	3 (2.6%)
Pancreas	3 (2.6%)
Uterus	2 (1.7%)
Nasopharynx	1(0.9%)
Others	10 (8.7%)
Histological subtypes	
Squamous cell carcinoma	37 (32.2%)
Adenocarcinoma	30 (26.1%)
Invasive ductal carcinoma	11 (9.6%)
Clear cell carcinoma	9 (7.8%)
Hepatocellular Carcinoma	5 (4.3%)
Small cell cancer	3 (2.6%)
Others	20 (13%)



**Figure 1. Survival Time of Patients with MAH**

diagnosis of cancer and occurrence of the hypercalcemia, level of serum calcium, symptoms and treatment regimes. The survival was assessed with the Kaplan-Meier method. The primary endpoint was the overall survival from the date of hypercalcemia episode.

*Statistical data analysis*

Statistical analysis was carried out with SPSS 18.0 software. Log-rank test was used to investigate the influence of variables on survival, and then a Cox proportional hazards model was established for multivariate analysis. Only variables with  $P < 0.1$  in the univariate analysis were selected for the multivariate analysis (Schwartz et al., 2005; Foussas et al., 2007).

**Results**

*Clinical characteristics of patients*

There were 76 males and 39 females, aged from 27~83 years old (median: 57 years old). All patients were at stage III or IV, except 2 cases of breast cancer

**Table 2. Prognostic Factors of Overall Survival (OS): Univariate Analysis with Log-rank Test**

Variables	n	Median OS (days)	P
All	115	50	
Male	76	50	0.002
Female	39	120	
Age $\geq$ 60	66	50	0.836
Age<60	49	50	
Squamous cell carcinomas	37	45	0.061
Other histological subtypes	78	76	
Bone met. (+)	53	46	0.320
Bone met. (-)	62	76	
Liver met. (+)	37	50	0.342
Liver met. (-)	78	73	
Lung met. (+)	37	50	0.738
Lung met. (-)	78	67	
Renal met. (+)	8	26	0.046
Renal met. (-)	107	59	
Number of metastasis sites $\geq$ 3	20	33	0.300
Number of metastasis sites<3	95	77	
Hypercalcemia >140 days after cancer diagnosis	60	44	0.009
Hypercalcemia $\leq$ 140 days after cancer diagnosis	55	94	
Serum calcium>3.4 mmol/L	24	45	0.597
Serum calcium $\leq$ 3.4 mmol/L	91	67	
Central nervous system symptoms (+)	29	15	0.000
Central nervous system symptoms (-)	86	94	
Bisphosphonates	31	50	0.017
Hydration and diuretic	63	244	

(stage II), 2 cases of colon cancer (stage II), 1 case of esophagus cancer (stage II), 3 cases of lung cancer (without staging information), 1 case of gingiva cancer (without staging information), 1 case of prostate cancer (without staging information) and 1 case of glans penis cancer (without staging information). Their characteristics were summarized in Table 1 and 2.

*Analysis on survival time and prognostic factors*

Metastases in the bone, liver, lung, kidney and brain were 53 cases (46.0%), 37 cases (32.2%), 37 cases (32.2%), 8 cases (7.0%) and 1 case (0.9%), respectively. The median time interval between the diagnosis of cancer and occurrence of hypercalcemia was 144 days (range: 1~3451 days). The median serum calcium level was 2.97 mmol/L (range: 2.77~4.87 mmol/L). There were 29 patients with central nervous system symptoms, including dysphoria, hypersomnia, dottiness, intermittent hallucination. Except for 9 cases who were death or discharged within 5 days after occurrence of hypercalcemia, all other patients recovered to normal blood calcium level after treatment with bisphosphonates or intravenous hydration and diuretics. Patients received intravenous hydration and diuretic (n=33, 28.7%) and bisphosphonates (n=63, 54.8%) treatment.

The median survival time of the entire cohort was 50 days (range: 1~4051 days) (Figure 1). The following variables were found to be poor prognostic factors in univariate analysis: the male, renal metastasis, central nervous system symptoms and hypercalcemia >140 days

**Table 3. Prognostic Factors of OS: Multivariate Analysis with Cox Model**

Variables	P	Hazard ratio	95%CI
Male	0.027	2.131	1.088~4.174
Hypercalcemia >140 days after cancer diagnosis	0.001	2.403	1.417~4.074
Central nervous system symptoms	0.002	3.054	1.530~6.096

**Table 4. Median OS according to Prognostic Factor Scoring**

Score	n (%)	Median OS (days)
0	11 (9.6%)	1067
1	37 (32.2%)	132
2	36 (31.3%)	34
3	31 (30.0%)	8

after cancer diagnosis. Although the patients treated with bisphosphonates had a shorter median OS compared to those treated with hydration and diuretic (244 days vs. 50 days) ( $P=0.017$ ), we supposed it might not be a poor prognostic factor for the bias of the data. For example, the media serum calcemia of the patients treated with bisphosphonates was higher than that of the patients treated with hydration and diuretic (3.13 mmol/L vs. 2.89 mmol/L) and the patients with serum calcemia >3.4 mmol/L were all treated with bisphosphonates. Variables with  $P<0.1$  were selected for the multivariate analysis. Serum calcemia was selected for the multivariate analysis, although  $P$  value was above 0.05 ( $P=0.597$ ). In multivariate analysis, three independent variables remained significant: the male ( $RR=2.131$ ,  $P=0.027$ ), central nervous system symptoms ( $RR=3.054$ ,  $P=0.002$ ), and hypercalcemia >140 days after cancer diagnosis ( $RR=2.403$ ,  $P=0.001$ ) (Table 3).

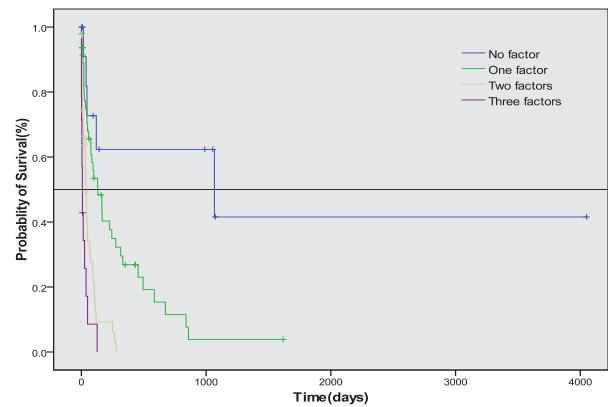
#### Median OS according to prognostic factor scoring

The patients were grouped according to the three independent predicting factors: score=0 (absence of independent predicting factor), score=1 (presence of one independent predicting factor), score=2 (presence of two independent predicting factors), and score=3 (presence of three independent predicting factors). Median survival time of patients with scores 0, 1, 2, and 3 were 1 067, 132, 34, and 8 days, respectively ( $P=0.000$ ) (Table 4, Figure 2). Obviously, the survival time decreased with the increase of the number of the poor prognostic factors.

## Discussion

MAH, defined by serum calcium over 2.75 mmol/L, is one of the clinical emergencies in medical oncology, often arising at the late stage of disease. The prevalence of MAH is around 3%~30% of all cancer patients (Grill et al., 2000; Stewart et al., 2005; Buchner-Daley et al., 2012; Hassan et al., 2012; Sookprasert et al., 2012). However, the incidence of MAH in China is far below the number (Xie et al., 2006; Shi et al., 2008). In our study, it was only 1.42%. Until now, there are no related explanation of this difference. Hypercalcemia is classified to three grades according to the serum calcium, mild (2.75~3.0 mmol/L), moderate (3.0~3.4 mmol/L) and severe (>3.4mmol/L).

There are two main proposed mechanisms for this



**Figure 2. Survival of Patients with MAH according to Selected Prognostic Factors.** The patients were classified according to the number of involved independent predicting factors: the male, central nervous system symptoms and hypercalcemia >140 days after cancer diagnosis. Score=0 (absence of independent predicting factor), score=1 (presence of one independent predicting factor), score=2 (presence of two independent predicting factors), and score=3 (presence of three independent predicting factors)

disorder. Production of humoral factors by the primary tumor, such as parathyroid hormone-related protein (PTHrP), infrequent tumor production of 1, 25-(OH)<sub>2</sub>D and parathyroid hormone, is responsible for 80% of the MAH cases. The remaining 20% of cases is caused by osteoclast bone resorption locally induced by bone metastasis (Clines et al., 2011). Yet, sometimes, the production of PTHrP and bone lysis co-works for MAH in a patient. Therefore, it is partially explained the fact that the extent of bone involvement seen at bone scintigraphy may not be correlated with the severity of hypercalcemia. Recent investigations have revealed that interactions between osteoclasts and cancer cells are mainly mediated by PTH-rP (Lumachi et al., 2009). PTH-rP stimulates osteoclasts to release receptor activator of nuclear factor-kappa ligand (RANKL) and osteoclast precursors. The RANK-RANKL interaction triggers several intracellular pathways involving most important nuclear factors such as (NF)-kappa B, c-Jun N-terminus kinase (JNK) and p38 mitogen-activated protein tyrosine kinase (MAPK), inducing differentiation, activation and prolonged survival of osteoclasts (Tanaka et al., 2005; Neville-Webbe et al., 2010). Gwendolen, et al. reported that the calcium-sensing receptor (CaR) was a critical factor for the rapid development of MAH in patients with lung small cell cancer, which may be a potential mechanism and a potential therapeutic target (Gwendolen et al., 2011). The underlying pathophysiological mechanisms of MAH are more complex and heterogeneous than currently known.

The symptoms of MAH vary and are difficult to be distinguished from that of the underlying disease or the side effects of cancer therapy, such as fatigue, nausea

and vomiting, renal insufficiency, ECG alterations and the central nervous system symptoms etc. In our study, the central nervous system symptom had been confirmed as an independent prognostic factor for the outcome of cancer patients with MAH.

Key therapies to MAH in cancer patients are intravenous hydration and diuretics to promote calciuresis and bisphosphonates to reduce pathologic osteoclastic bone resorption (Ding et al., 2013). Calcitonin and glucocorticoids are also able to lower the calcium level in the circumstance of 1, 25-(OH)<sub>2</sub>D-mediated hypercalcemia. In term of potency, bisphosphonates ranks as follows: zoledronate >risedronate >ibandronate >alendronate >pamidronate (Li et al., 2011). In our study, the patients treated with bisphosphonates had a shorter median OS compared to those treated with hydration and diuretic (244 days vs. 50 days,  $P=0.017$ ), but we supposed that the bias still existed in the data. For example, the serum calcemia of the patients treated with bisphosphonates was higher than that of the patients treated with hydration and diuretic (media serum calcemia: 3.13 mmol/L vs. 2.89 mmol/L), while they were supposed to be basically equal. Moreover, the patients with serum calcemia >3.4 mmol/L, who were supposed to have a poor prognosis, were all treated with bisphosphonates. This bias may mask the efficacy of bisphosphonates to some extent. Besides, the Cox model did not identify the bisphosphonates treatment as an independent factor for poor prognosis of patients with MAH.

There are some novel strategies to treat MAH. Denosumab (AMG162), a fully human monoclonal IgG2 antibody, targets the RANK-RANKL pathway and has been demonstrated to inhibit bone resorption in osteoporosis and bone metastases with a very good profile of tolerability (Body et al., 2006; Stopeck et al., 2009; Neville-Webbe et al., 2010). A recombinant version of osteoprotegerin (OPG) showed the ability to suppress the activity of RANKL in vitro and both to prevent MAH and normalize bone turnover in mice (Croucher et al., 2001; Morony et al., 2005). There are other new agents currently under evaluation: a humanized anti-PTHrP antibody, tyrosine-kinase inhibitors such as dasatinib, cathepsin K inhibitor Odanacatib, endothelin 1 inhibitor atrasentan, monoclonal antibodies against DKK1 or Activin A (Sato et al., 2003; Body et al., 2010; Vallet et al., 2010).

Despite an adequate intravenous therapy, life expectancy of patients with MAH remains poor, with a median survival of 50 days in our series. In our study, the multivariate analysis identified the following factors as predictors of poor survival: the male, central nervous system symptoms, and hypercalcemia occurring over 7 weeks after cancer diagnosis. The most potent predictive factor of short survival was the central nervous system symptoms. Patients with central nervous system symptoms had a much shorter median survival (15 days) than patients without these symptoms (94 days). The correlation between squamous cell carcinoma and the poor survival of patients with MAH has been previously reported (Lazaretti-Castro et al., 1993; Penel et al., 2008; Teo et al., 2008). In our study, although the Cox model did not identify the squamous cell carcinoma as an independent

prognostic factor for OS, univariate analysis revealed a borderline  $P$  value ( $P=0.061$ ) that patients with squamous cell carcinoma had a shorter median OS than patients with other histological subtypes (45days vs. 76days), which was consistent with previous reports (Penel et al., 2008). Furthermore, reports have indicated that higher serum calcium levels in MAH patients predict poorer survival outcome (Truong et al., 2003; Le et al., 2011). In our study, there was a trend that patients with serum calcium >3.4 mmol/L presented poorer prognosis than those  $\leq 3.4$  mmol/L (media OS: 45 days vs. 67 days), but the  $P$  value was 0.597 in the univariate analysis. Cox model still failed to identify the serum calcium level as an independent prognostic factor. The imbalanced distribution and the relatively small number of the cohort may put limitations in the interpretation of the data. Most of the studies on this topic were flawed with this limitation for the low prevalence of MAH.

Moreover, we had built a simple predictive model aiming to identify these patients with very poor outcome. The median OS of patients presented with three predicting factors was only 8 days. It was obvious that the more independent predicting factors the patients presented, the poor prognosis they had.

Though our study presented several limitations due to its retrospective characteristics, such as lack of data on PTH-rP levels in the patients and failure to exclude the non-cancerous cause of hypercalcemia (such as primary hyperparathyroidism). This was the first relatively large scale analysis on the survival of patients with MAH in Chinese population. Because of the low frequency of MAH in the cancer population, we had screened 115 out of over 8 000 patients with MAH to make it a relatively larger sample size than previous reports. It provides valuable information for MAH patient's survival with prognostic factors. Besides, the score system can provide, to some degree, the reference for MAH prognosis and treatment.

In conclusion, the patients with MAH have a very poor median survival. The prognostic score developed in this study based on the gender, central nervous system symptoms, and hypercalcemia occurring time after cancer diagnosis, needs to be validated on an independent cohort. It will help to predict the patient's prognosis more exactly to design the treatment strategies.

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