RESEARCH ARTICLE

Prognostic Factors in Adult Patients with Solid Cancers and Bone Marrow Metastases

Yu-Shin Hung[1], Wen-Chi Chou[1]*, Tai-Di Chen[2], Tse-Ching Chen[2], Po-Nan Wang[1], Hung Chang[1], Hung-Chih Hsu[1], Wen-Chi Shen[1], Wei-Hong Cheng[3], Jen-Shi Chen[1]*

Abstract

Background: Solid cancers with bone marrow metastases are rare but lethal. This study aimed to identify clinical factors predictive of survival in adult patients with solid cancers and bone marrow metastases. Methods: A total of 83 patients were enrolled consecutively between January 1, 2000 and December 31, 2012. Bone marrow metastases were confirmed by biopsies. Patient clinical features and laboratory data were analyzed for associations. Results: The median age of the patients was 54 years (range, 23–88 years), and 58% were male. The 3 most common primary tumor locations were the stomach (32 patients, 39%), prostate (16 patients, 19%), and lungs (12 patients, 15%). The median overall survival was 49 days (range, 3–1423 days). Patients with Eastern Cooperative Oncology Group performance status 1, cancers of prostate origin, platelet counts over 50,000/ml, and undergoing antitumor therapies had a significantly better prognosis in the multivariate analysis. The median survival times were 173 and 33 days for patients with 2-3 more favorable parameters (n=24) and those with 0-1 (n=69), respectively (hazard ratio 0.30; 95% CI 0.17-0.52, $p<0.001$). Conclusions: Solid cancers with bone marrow metastases are dismal and incurable diseases. Understanding prognostic factors to these diseases helps medical personnel to provide appropriate treatments and better inform patients about outcomes. Antitumor therapies may improve outcomes in selected patient cohorts.

Keywords: Solid cancer - bone marrow metastasis - prognosis - antitumor therapy

Asian Pac J Cancer Prev, **15 (1)**, 61-67

Introduction

Solid cancer with bone marrow metastases is a rare but lethal condition (Ringenberg et al., 1986; Wang et al., 1987; Papac RJ, 1994; Ozkalemkas et al., 2005; Kim et al., 2007; Kwon et al., 2011). Bone marrow biopsy has been the standard diagnostic modality for overt bone marrow metastases arising from solid cancers since 1958 when McFarland and Dameshek first described a simplified technique for bone marrow biopsy (McFarland et al., 1958). The incidence of bone marrow metastases developing from solid cancers is difficult to define because bone marrow examination is not a routine staging procedure for patients with solid cancers; in addition, some patients are too sick to undergo the procedure at the time of suspicion of bone marrow metastasis. Therefore, only small cases series of patients with solid cancers and bone marrow metastases are reported in the literature. Among these reports, malignancies of the prostate, breast, lungs, and stomach were the primary tumors that most frequently metastasized to the bone marrow (Hansen et al., 1971; Shah et al., 1985; Ceci et al., 1988; Tritz et al., 1989; Diel et al., 1992; Trillet-Lenoir et al., 1994; Kim et al., 2007; Kwon et al., 2011; Mehdi et al., 2011).

Reports about the clinical features and outcomes of patients with solid cancers with bone marrow metastases are limited. The timing of the diagnosis and clinical presentation of overt bone marrow metastases in solid cancers varies widely. Patients may present with metastatic disease at the initial site (Wong et al., 1993; Xiao et al., 2009) or with sequelae of disseminated organ metastases. Bone marrow is not a visible organ, and patients with bone marrow metastases may present with bone pain and symptoms of bone marrow failure such as anemia, bleeding tendencies, and repetitive infections. In some cases, patients are asymptomatic with only abnormal hematogram findings (Ringenberg et al., 1986; Wong et al., 1993; Ozkalemkas et al., 2005) that are discovered incidentally during blood examinations for other reasons. The lack of a specific presentation makes the early diagnosis of bone marrow metastasis difficult and increases the difficulty of subsequent antitumor therapy. Patients with solid cancers and bone marrow metastases exhibit rapidly progressive clinical courses and die soon

*[1]Division of Hematology-Oncology, Department of Internal Medicine, [2]Department of Pathology, Chang Gung Memorial Hospital at Linkou, and School of Medicine, Chang Gung University, Taoyuan, [3]Division of Hematology and Oncology, Departement of Internal Medicine, Taipei Medical University-Shung Ho hospital, Ministry of Health and Welfare, Taipei, Taiwan *For correspondence: wenchi3992@yahoo.com.tw, js1101@adm.cgmh.org.tw*

because of disseminated cancer or complications of bone marrow failure. It poses a great challenge to clinicians to institute appropriate antitumor therapies for these patients with the goals of both prolonging survival and alleviating symptoms.

To optimize patient outcome, clinicians must balance the efficacy and toxicity of therapy to maximize the antitumor response and minimize bone marrow suppression. Unfortunately, the result of therapy is often unsatisfactory because these patients are commonly refractory to conventional treatment. Most patients receive only supportive care because all available antitumor treatments have been exhausted or because they were too weak to receive antitumor therapy. The benefit of systemic antitumor therapies in these patients remains to be an issue of debate.

Despite the improvement of modern medicine in the 21th century, the prognosis of patients with solid cancers and bone marrow metastases remains unsatisfactory. In this study, we retrospectively analyzed the clinical features, primary cancer types, laboratory examinations, pathologic changes in bone marrow specimens, treatment modalities, and outcomes of patients with solid cancers and overt bone marrow metastases proven by bone marrow biopsy. We aimed to identify favorable parameters in these patients and assess the role of antitumor therapies in patients with these parameters.

Materials and Methods

Patient selection

Patients were enrolled consecutively from among those admitted to Chang Gung Memorial Hospital (CGMH) at Linkou between January 1, 2000, and December 31, 2012. All diagnoses of bone marrow metastases were confirmed by bone marrow examination as per the institute database. Patients with hematologic malignancies, including lymphoma, leukemia, and myeloma, and those less than 18 years old were excluded from the study. The study was approved by the ethics committee of the institute.

Data collection

Data on patient demographics, primary tumor location, cancer histological type and differentiation, Eastern Cooperative Oncology Group performance status (ECOG PS), clinical symptoms, peripheral blood and biochemistry test findings at the time of diagnosis of bone marrow metastases, the use of systemic antitumor therapy and the treatment response, and survival time and most likely cause of death were collected. Each bone marrow biopsy specimen was reviewed by a single pathologist to evaluate the presence and degree of bone marrow necrosis, tumor necrosis, bone marrow fibrosis, and peripheral bone reaction with intent to correlate bone marrow pathologic characteristics with patient outcome.

Bone marrow metastasis was considered to be present at the initial diagnosis of disseminated cancer or relapsed cancer if bone marrow metastasis was diagnosed before or within 2 weeks after the primary cancer or relapsed cancer diagnosis. Systemic antitumor therapy was defined as cytotoxic chemotherapy, targeted therapy, or hormone therapy designed to exert an antitumor effect. The antitumor response was categorized according to Response Evaluation Criteria in Solid Tumors Criteria 1.1 (Eisenhauer et al., 2009). For patients who received more than 2 lines of antitumor therapy, the response represented the best tumor response to multiline antitumor treatment. The response was categorized as progressive disease if the patient died during the course of antitumor treatment or before imaging studies for response evaluations were conducted. The survival time was calculated from the date of bone marrow biopsy to the date of death. The cause of death was categorized as follows: cancer with organ failure (such as hepatic failure or respiratory failure by tumor infiltration), sepsis (defined as overt infection within 3 days of death), or sequelae of hemorrhage or embolism (such as pulmonary hemorrhage, intracranial hemorrhage, or systemic embolism). The dates of the primary cancer diagnosis, diagnosis of bone marrow metastasis, and death of each patient were obtained from either the cancer registration center in our institute or the National Register of Death Database in Taiwan. All the patients were followed-up until death or the end of this study on December 31, 2012.

Statistical analysis

Statistical analyses were performed using SPSS 17.0 statistics software (SPSS Inc, Chicago, USA). Basic demographic data were summarized as n (%) for categorical variables and medians for continuous variables. Survival time was calculated using the Kaplan-Meier method. Univariate and multivariate analysis of overall survival for all clinical characteristics of patients was performed using the log-rank test and Cox's proportional hazard model. The characteristics associated with significant differences in overall survival as identified by univariate analysis were subsequently used for multivariate analysis. Patients were further categorized according to the numbers of better prognostic factors presented. Hazard ratio was estimated using unstratified Cox's regression. All statistical assessments were considered significant at $p < 0.05$.

Results

A total of 83 patients were included in this study (Table 1). The median age of the patients was 54 years (range, 23–88 years), and 58% of the patients were male. Twenty-two (27%) patients had an ECOG PS of 1, whereas 26 (31%), 22 (27%) and 13 (15%) patients had an ECOG PS of 2, 3 and 4, respectively. The 3 most common primary tumor locations were the stomach (32 patients, 39%), prostate (16 patients, 19%), and lungs (12 patients, 15%). Seven (8%) patients were diagnosed with primary cancers of unknown origin. All cancers exhibited an adenocarcinomatous histology, and 70 patients (85%) had poorly differentiated tumors. The median interval between the diagnosis of primary tumor and that of bone marrow metastasis was 65 days (range, 0–2661 days). Bone marrow metastases were present at the initial diagnosis of disseminated cancer and at the diagnosis of relapsed cancer in 32 (39%) and 9 (11%) patients, respectively.

Table 1. Characteristics of Patients with Solid Cancer and Bone Marrow Metastases

Variable	No. of patients (%), n = 83
Age, median (range)	54 (23–88)
Male gender	48 (58)
ECOG performance status	
1	22 (27)
2	26 (31)
3	22 (27)
4	13 (15)
Primary tumor location	
Stomach	32 (39)
Prostate	16 (19)
Lung	12 (15)
Breast	9 (11)
Colorectum	7 (8)
Unknown origin	7 (8)
Histological differentiation of primary tumor	
Well-differentiated	2 (2)
Moderately differentiated	11 (13)
Poorly differentiated	70 (85)
Median interval between diagnoses of primary tumor and bone marrow metastases, days (range)	65 (0–2661)
Bone marrow metastases present at initial diagnosis of disseminated cancer	32 (39)
Bone marrow metastases present at initial diagnosis of relapsed cancer after curative therapy	9 (11)

ECOG, Eastern Cooperative Oncology Group

The clinical manifestations at the time of diagnosis of bone marrow metastases are presented in Table 2. Bone pain (63%) was the most common symptom, followed by fever (36%) and active bleeding (22%). Regarding abnormal hematogram findings, anemia (95%) was the most common finding, followed by thrombocytopenia (77%), leukocytosis (31%), leukopenia (18%), and neutropenia (12%). Pancytopenia was present in 13% of all patients, and only 1 (1%) patient presented with a normal blood count. Sixty-six (80%) patients had immature cells in their peripheral blood, and immature white blood cells (leukoblastosis), nucleated red blood cells (erythroblastosis), and both (leukoerythroblastosis) were present in the peripheral blood of 77%, 63%, and 60% of patients respectively. Twenty-two patients (27%) were diagnosed with microangiopathic hemolytic anemia (MAHA). Prolonged prothrombin times (international normalized ratio [INR] >1.2-fold greater than normal controls) were detected in 33 of 67 patients. Concerning biochemistry findings, elevated alkaline phosphatase (ALP) content was the most common abnormal finding (91%), and 53% of the patients had extremely high ALP levels (>5-fold of the upper normal limit). Other common abnormal serum findings present in more than 50% of patients were elevated lactate dehydrogenase (LDH) levels (89%), elevated carcinoembryonic antigen (CEA) levels (60%), hypoalbuminemia (53%), and elevated aspartate aminotransferase (AST) levels (53%). Bone marrow biopsy specimens were available for 80 patients, and these were reviewed retrospectively by a single pathologist. Viable tumor cells were present in all bone marrow biopsy specimens. Other abnormal findings in bone marrow biopsy specimens were peripheral bone reactions (68%), bone marrow fibrosis (60%), tumor necrosis (33%), and bone marrow necrosis (16%).

Table 2. Clinical and Laboratory Findings at Detection of Bone Marrow Metastases in Patients with Solid Cancers

Variables	No. of patients/ total no. of patients (%)
Clinical symptoms	
Bone pain	52/83 (63)
Fever	30/83 (36)
Bleeding	18/83 (21)
Presence of abnormal cells in peripheral blood	
Anemia	79/83 (95)
Thrombocytopenia	64/83 (77)
Leukocytosis	26/83 (31)
Leukopenia	15/83 (18)
Neutropenia (absolute neutrophil count < 1500/m^3)	10/83 (12)
Pancytopenia	11/83 (13)
None	1/83 (1)
Presence of immature cells in peripheral blood	
Leukoblastosis	64/83 (77)
Erythroblastosis	52/83 (63)
Leukoerythroblastosis	50/83 (60)
None	17/83 (20)
Presence of MAHA	22/83 (27)
Prolonged coagulation (prothrombin time, INR > 1.2)	33/67 (50)
Abnormal biochemistry findings	
Elevated ALP >1-fold of UNL	71/78 (91)
>5-fold of UNL	41/78 (53)
Elevated LDH >1-fold of UNL	25/28 (89)
Elevated CEA level >1-fold of UNL	33/55 (60)
Hypoalbuminemia (albumin < 3.5 g/dL)	39/74 (53)
Elevated AST >1-fold of UNL	42/79 (53)
Elevated total bilirubin >1-fold of UNL	17/73 (23)
Elevated BUN >1-fold of UNL	9/74 (12)
Elevated creatinine >1-fold of UNL	5/81 (6)
Hypercalcemia (Ca > 10 mg/dL)	2/71 (3)
Hypocalcemia (Ca < 8 mg/dL)	14/71 (20)
Bone marrow findings	
Presence of viable tumor cells	80/80 (100)
Presence of bone marrow necrosis	13/80 (16)
Presence of bone marrow fibrosis	48/80 (60)
Presence of presence with tumor necrosis	26/80 (33)
Presence of peripheral bone reaction	54/80 (68)

MAHA, microangiopathic hemolytic anemia; INR, international normalized ratio; ALP, alkaline phosphatase; UNL, upper normal limit; LDH, lactate dehydrogenase; CEA, carcinoembryonic antigen; AST, aspartate aminotransferase; BUN, blood urea nitrogen

The median overall survival was 49 days (range, 3–1423 days). At the conclusion of this study only one patient was still alive with a survival of more than 470 days. The main causes of death were sepsis (53/82, 65%), sequelae of hemorrhage or embolism (19/82, 23%), and cancer with organ failure (10/82, 12%).Thirty-three (40%) patients received supportive care only. The remaining 50 (60%) patients received antitumor therapy, and a clinical benefit was reported in 40% (20/50) of these patients: partial response in 24% of patients and stable disease in 16% of patients. The remaining 60% (30/50) of patients had progressive disease. In patients having solid cancers other than prostate cancers, 16.7% (7/42) of patients had partial response, 16.7% (7/42) had stable diseases and

Table 3. Univariate and Multivariate Analyses of Overall Survival According to the Clinical Variables

Variables	Category	No. of patients	Median survival (95% CI)	Univariate *p* value	Hazard ratio (95% CI)	Multivariate *p* value	Adjusted hazard ratio (95% CI)
ECOG	1	22	228 (103.9–352.1)	<0.000	0.08 (0.03–0.18)	<0.000	0.14 (0.05–0.38)
PS	2	26	61 (48.0–74.0)	<0.000	0.27 (0.13–0.55)	0.12	0.49 (0.19–1.22)
	3	22	27 (20.1–33.9)	0.044	0.48 (0.24–0.98)	0.69	0.84 (0.36–1.98)
	4	13	16 (0.7–31.3)	Reference	1	Reference	1
Primary	Stomach Prostate	32	44 (24.0–63.9)	Reference	1	Reference	1
tumor	Lung	16	139 (0–307.6)	0.007	0.40 (0.20–0.77)	<0.000	0.20 (0.08–0.48)
location	Breast	12	22 (10.1–33.9)	0.69	1.14 (0.59–2.23)	0.45	0.73 (0.32–1.66)
	Colorectum	9	73 (0–172.3)	0.25	0.64 (0.30–1.37)	0.56	0.74 (0.27–2.04)
	Unknown	7	66 (24.9–107.1)	0.241	0.59 (0.25–1.42)	0.11	0.46 (0.18–1.19
		7	28 (12.6–43.4)	0.134	1.89 (0.82–4.37)	0.38	0.74 (0.28–1.93
MAHA	Yes	22	38 (15–61)	Reference	1	Reference	1
	No	61	58 (34–82)	0.029	0.57 (0.34–0.94)	0.44	0.68 (0.26–1.79)
Platelet	<50 ×10^3/mm^3	27	33 (16–50)	Reference	1	Reference	1
count	>50 ×10^3/mm^3	56	66 (40–92)	0.002	0.47 (0.30–0.76)	0.006	0.40 (0.21–0.78)
Total	>1 × UNL	21	38 (13–63)	Reference	1	Reference	1
bilirubin	<1 × UNL	52	62 (17–107)	0.007	0.49 (0.29–0.83)	0.36	0.36 (0.24–2.00)
Antitumor	No	33	21 (13–29)	Reference	1	Reference	1
therapy	Yes	50	87 (2.7–171)	<0.000	0.34 (0.22–0.54)	0.005	0.35 (0.17–0.73)

ECOG, Eastern Cooperative Oncology Group; MAHA, microangiopathic hemolytic anemia

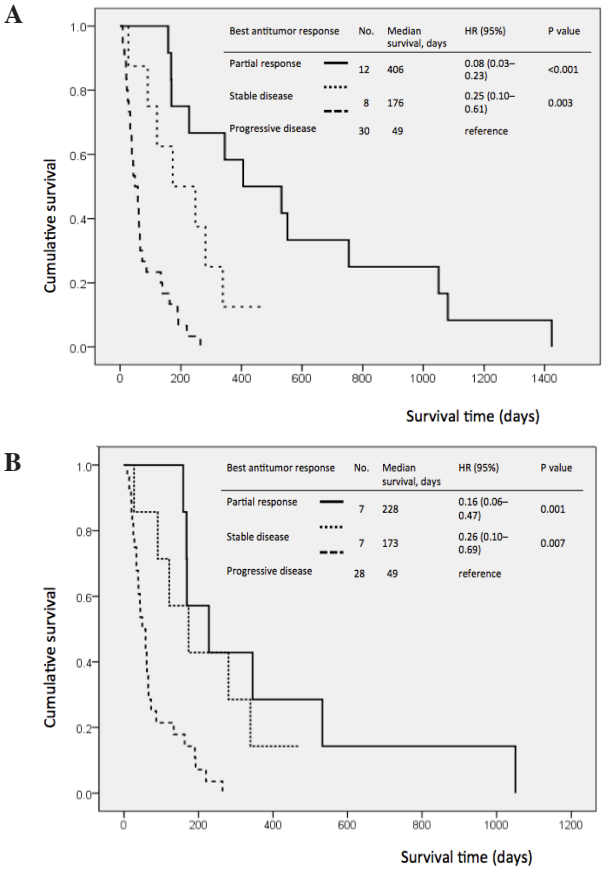

Figure 1. Survival Time in Different Groups Based on Their Responses to Antitumor Therapies Was Shown in Figure 1A, for All Patients (n = 50), and in Figure 1B, for All Non-prostate Cancer Patients (n = 42)

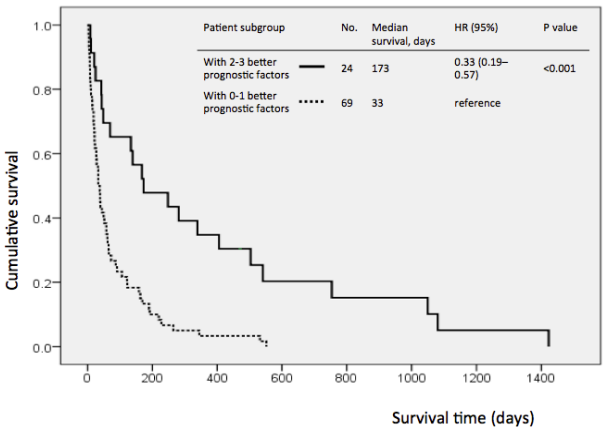

Figure 2. Subgroup Analysis for Survival Time According to the Numbers of Better Prognostic Factors Presented in All Patients (n=83)

66.7% (28/42) had progressive diseases. Survival time in different groups based on their responses to antitumor therapies was shown in Figure 1A, for all patients (n = 50), and in Figure 1B, for all non-prostate cancer patients (n = 42).

The results of univariate and multivariate analyses of survival associated with clinical variables are presented in Table 3. Only clinical variables associated with significant differences in survival are shown. The positive prognostic factors that significantly influenced overall survival in univariate analysis were ECOG PS (ECOG PS 1: median survival, 228 days; hazard ratio [HR] = 0.08; 95% confidence interval [CI] = 0.03–0.18; ECOG PS 2: median survival, 61 days; HR = 0.27; 95% CI = 0.13–0.55; ECOG PS 3: median survival, 27 days; HR = 0.48; 95% CI = 0.24–0.98; ECOG PS 4: median survival, 16 days [reference]), primary tumor location from prostate (vs. stomach: median survival, 139 days vs. 44 days; HR = 0.40; 95% CI = 0.20–0.77), presence without MAHA (median survival 58 days vs. 38 days; HR = 0.57; 95% CI = 0.34–0.94), platelet counts ≥50 × 10^3/mm^3 (median survival, 66 days vs. 33 days; HR = 0.47; 95% CI = 0.30–0.76), total bilirubin level within normal limit (median survival, 62 days vs. 38 days; HR = 0.49; 95% CI = 0.29–0.83), and receive antitumor therapy (median survival, 87 days vs. 821 days; HR = 0.34; 95% CI = 0.22–0.54). No difference in survival related to tumor histological differentiation and the presence of any abnormal bone marrow finding was noted. ECOG PS 1

Table 4. Previously Reported Clinical Features and Outcomes of Patients with Solid Cancer and Bone Marrow Metastases

Author	Patient number	Cancer type	Clinical manifestations	Hematogram (%)	Median overall survival (days)	Positive prognostic factor (median overall survival)
Wang et al, 1987	96	Unknown primary origin (29%) Nasopharynx (25%) Stomach (14%)	Bone pain (78%) Fever (40%)	Anemia (84%) Leukoblastosis (84%) Erythroblastosis (49%)	35	Use of antitumor treatment (95 days)
Ozkalemks et al, 2005	19	Stomach (26%) Unknown primary origin (26%)	Bone pain (47%) Bleeding (16%)	Anemia (100%) Thrombocytopenia (100%) Leukoerythroblastosis (79%)	37	Not available
Kin et al, 2007	39	Stomach (100%)	Bone pain (44%) Bleeding (20%)	Not available	44	Absence of hyponatremia (Na < 133 mmol/L), lung metastasis, and peritoneal seeding (67 days)
Mehdi et al, 2011	31	Prostate (29%) Breast (26%) Stomach (16%)	Not available	Anemia (71%) Thrombocytopenia (45%)	Not available	Not available
Kwon et al, 2011	26	Stomach (100%)	Not available	Not available	37	Chemotherapy (121 days) ALT ≤ 31 IU/L (118 days)
This study	83	Stomach (39%) Prostate (19%) Lung (15%)	Bone pain (63%) Fever (36%) Bleeding (21%)	Anemia (95%) Thrombocytopenia (77%) Leukoblastosis (77%) Erythroblastosis (63%)	45	ECOG PS 1 (228 days) Antitumor therapy (87 days) Prostate origin (139 days) Platelet count > 50000 (66 days)

(ECOG PS 4: adjusted HR = 0.14; 95% CI = 0.05–0.38), primary tumor location from prostate (vs. stomach: adjusted HR = 0.20; 95% CI = 0.08–0.48), platelet count $\geq 50 \times 10^3/mm^3$ (adjusted HR = 0.40; 95% CI = 0.21–0.78), and receive antitumor therapy (adjusted HR = 0.35; 95% CI = 0.17–0.73) were significant prognostic factors in multivariate analysis. No patient presented with all 4 better prognostic factors; while 1 (1%) patients had 3, 22 (27%) patients had 2, 35 (42%) patients had 1 and 25 (30%) patients had 0 better prognostic factor. The median survival time was 173 and 33 days for patients with 2-3 more favorable parameters (n = 24) and those with 0-1 (n = 69), respectively (hazard ratio 0.30; 95% CI 0.17-0.52, $p<0.001$) (Figure 2).

Discussion

This study describes the clinical features of patients with solid cancers and bone marrow metastases at a medical center over 12 years in Taiwan. Patients were slightly younger than the median age of deceased patients with cancer in Taiwan (61 years in 2009) (Taiwan Health Registry Annual Report, 2009). Primary tumors in the stomach, prostate, and lungs constituted the most common solid cancers with bone marrow metastases. Most patients presented with symptoms related to bone marrow infiltration such as multiple bone pain, fever, and bleeding tendencies. Cytopenia, leukoerythroblastosis, and extremely high ALP levels were the most common abnormal laboratory findings. The clinical manifestations closely resembled those of previously published reports (Table 4).

The tumor pattern in this study was similar to those in reports from Western countries, but the findings differed greatly from those of 2 cohorts in our institute. Wang et al. (1987) reported an analysis of 96 patients with solid cancers and bone marrow metastases who visited our institute between 1980 and 1987. Twenty-eight (29%) patients were diagnosed with primary cancers of unknown origin, and tumors of the nasopharynx (25%) and stomach (13%) were also common. Additionally, 30% of patients had a nonadenocarcinomatous histology (including nasopharyngeal cancer and small cell lung cancer). In the current study, all tumors had an adenocarcinomatous histology, and no primary tumor arising from the nasopharynx was identified. The possible explanations were as follows. First, selection bias may have existed, although bone marrow examination was a standard diagnostic tool for detecting solid cancer with bone marrow metastases, and the invasive nature of the procedure may make patients or physicians reluctant to use it, especially for terminally ill patients who would not benefit from the confirmation of bone marrow metastases and for patients with certain cancer types for which the presence of leukoerythroblastosis is considered a surrogate diagnostic marker for bone marrow metastases (Burkhardt et al., 1981; Papac et al., 1994; Sar et al., 2001). A second explanation is the improved diagnostic modalities for detecting primary tumor, resulting in a decrease in the incidence of primary cancer of unknown origin from 29% to 8%. Finally, the incidence of nasopharyngeal cancer decreased gradually with the availability of effective radiotherapy and chemotherapy for nasopharyngeal cancer in Taiwan, and this could be a possible explanation (Al-Sarraf et al., 1988; Taiwan Health Registry Annual Report, 2009). Though there was much progress in advancing cancer treatment in the past decade, bone marrow metastases in patients with solid cancers remain a dismal and incurable condition. However, improved effective early antitumor treatment may decrease the incidence of bone marrow metastasis. For example, nasopharyngeal carcinoma is no longer one of the leading cancers with bone marrow metastases because of the much improved early treatment compared with what in two decades ago.

The prognosis of patients with solid cancers and bone marrow metastases was dismal in this study, in line with previous reports (Ringenberg et al., 1986; Wang et al., 1987; Ozkalemkas et al., 2005; Kim et al., 2007; Kwon et al., 2011). In addition to the use of antitumor treatment as identified in previous studies, our study identified 3 additional clinical factors predictive of survival in these patients groups: ECOG PS, primary tumor location, and platelet counts. Performance status is an important prognostic factor for patients with solid cancers and bone marrow metastases. Patients with poor performance statuses potentially have large tumor burdens,

complications due to acute severe illness, associated comorbidities, or limited access to antitumor therapy. All of these reasons may explain the poor prognosis of patients with poor performance statuses.

Thirty-two patients presented with bone marrow metastases at the initial diagnosis of disseminated cancer in this study, and the primary tumor location was not identified in 7 of these patients (7/32, 22%). In a previous study in our institute by Wang et al. (1987), 28 of 47 patients (60%) presented with metastatic bone marrow disease for which the location of the primary tumor was not identified. Despite dramatic improvements in modern medicine and examinational techniques, the primary tumor cannot be identified in all patients. There was no difference in survival associated with primary cancer location except in the case of prostate cancer. Before making a diagnosis of primary cancer of unknown origin with bone marrow metastasis, a prostate origin must be excluded. An indolent clinical course, the vulnerability of cancer cells to hormone therapy, and the toxicity profiles of hormone agents result in better survival among patients with prostate cancer and bone marrow metastases.

Our results showed that the main causes of death in patients with solid cancers and bone marrow metastases were complications of bone marrow failure, and sepsis and sequelae of hemorrhage or embolism caused 88% of the deaths in this patient group. MAHA, severe thrombocytopenia (platelet counts less than $50 \times 10^3/mm^3$), and elevated total bilirubin levels were negative prognostic factors in univariate analysis, whereas thrombocytopenia remained significantly associated with survival in multivariate analysis. The interim analyses showed that patients with MAHA or severe thrombocytopenia had a significantly higher risk of death due to sequelae of bleeding or thromboembolism than those without MAHA or thrombocytopenia. These results highlight the value of correlating laboratory data with prognosis and the possible cause of death. They also serve as a reminder for clinicians to routinely perform coagulation profile analysis in every patient with solid cancer and bone marrow metastases and to manage bleeding or thromboembolism events urgently and aggressively in patients with coagulopathy or severe thrombocytopenia.

In line with published reports (Wang et al, 1987; Kwon et al., 2011), antitumor therapy was a positive prognostic factor in our study, and the benefit was greater in patients with a partial response or stable disease. With the advancement in oncology, both in targeted and systemic chemotherapies, we anticipate that there will be similar results for other cancers as in the case of prostate cancers. To prolong life expectancy, antitumor therapy should recommend for all patients with solid cancers and bone marrow metastases. However, only 40% patients of all cancer types, and 33.3% of non-prostate cancer patients benefited from antitumor therapies. It is important to select patients who will potentially benefit from antitumor therapies. Our findings identified some prognostic factors to aid in patient selection. One major finding was that patients presented with 2-3 favorable prognostic factors had significantly better survival results than those with 0-1 factors. For patients presented with antitumor therapy as the only favorable prognostic factor, their survival did not improve with antitumor therapies. In contrary, patients presented with at least one favorable prognostic factor other than antitumor therapy, they are more likely to benefit from antitumor therapies.

Previous studies reported that the presence of bone marrow necrosis was a poor prognostic factor in patients with cancer (Dunn et al., 1993; Forrest et al., 2000; Paydas et al., 2002). Therefore, pathologic changes in bone marrow specimens were reviewed to correlate pathologic findings other than the presence of tumor cells with patient outcome in the current study. Neither the presence nor severity of bone marrow fibrosis, bone marrow necrosis, tumor necrosis, or peripheral bone reaction affected patient outcome. In previous studies (Dunn et al., 1993; Forrest et al., 2000; Paydas et al., 2002), bone marrow necrosis typically accompanied bone marrow metastases, and thus, the poor prognosis of these patient groups resulted from bone marrow metastases rather than bone marrow necrosis. Our study did not illustrate the prognostic value of bone marrow necrosis in patients with solid cancers and bone marrow metastases.

Our study had some limitations. First, this was a retrospective study performed at a single site, and cases of bone marrow metastases were confirmed by bone marrow examinations; therefore, the study result did not include the characteristics of patients with occult bone marrow metastases or clinically suspicious patients who did not undergo bone marrow examination. Second, validation of the prognostic factors identified in this study was limited by the small sample size. Third, because of the wide variation in components of solid cancer and antitumor therapy, including cytotoxic chemotherapy, hormone therapy, molecular-targeted therapy, and combination therapy with 2 of these treatments, no further detailed analyses of antitumor strategies were possible. Well-designed multisite, prospective studies are necessary to address these limitations.

In conclusion, Bone marrow metastases in patients with solid cancers remain a dismal and incurable condition. Herein we described clinical characteristics of solid cancer patients with bone marrow metastases and identified ECOG PS, primary tumor location, platelet counts and antitumor therapies as important predictors for more favorable survival. Understanding prognostic factors to these diseases helps medical personnel to provide appropriate treatments and better inform patients about outcomes. Antitumor therapies improve outcomes in select patient cohorts.

Acknowledgements

The authors thank all the members of the Cancer Center, Chang Gung Memorial Hospital, for their invaluable help. The author(s) declare that they have no competing interests.

References

Al-Sarraf M, LeBlanc M, Giri PG, et al (1988). Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal

cancer: phase III randomized Intergroup study 0099. *J Clin Oncol,* **16**, 1310-7.

Burkhardt R, Frisch B, Bartl R, et al (1981). Detection of haematologic and nonhaematologic cancer by bone biopsy. *Cancer Detect Prev*, **4**, 619-27.

Ceci G, Franciosi V, Passalacqua R, et al (1988). The value of bone marrow biopsy in breast cancer at the time of first relapse: a prospective study. *Cancer*, **61**, 1041-5.

Diel IJ, Kaufmann M, Goemer R, et al (1992). Detection of tumor cells in bone marrow of patients with primary breast cancer: a prognostic factor for distant metastases. *J Clin Oncol*, **10**, 1534-9.

Dunn P, Shih LY, Liaw SJ, Sun CF (1993). Bone marrow necrosis in 38 adult cancer patients. *J Formos Med Assoc*, **92**, 1107-10.

Eisenhauer EA, Therasse P, Bogaerts J, et al (2009). New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*, **45**, 228-47.

Forrest DL, Mack BJ, Nevill TJ, et al (2000). Bone marrow necrosis in adult acute leukemia and non-Hodgkin's lymphoma. *Leuk Lymphoma*, **38**, 627-32.

Hansen HH, Muggia FM, Selawry OS (1971). Bone marrow examination in 100 consecutive patients with bronchogenic carcinoma. *Lancet*, **2**, 443-5.

Kim HS, Yi SY, Jun HJ, et al (2007). Clinical outcome of gastric cancer patients with bone marrow metastases. *Oncology*, **73**, 192-7.

Kwon JY, Yun J, Kim HJ, et al (2011). Clinical outcome of gastric cancer patients with bone marrow metastases. *Cancer Res Treat*, **43**, 244-9.

McFarland W, Dameshek W (1958). Biopsy of bone marrow with the Vim-Silverman needle. *JAMA*, **166**, 1464-6.

Mehdi SR, Bhatt ML (2011). Metastasis of Solid Tumors in Bone Marrow: A Study from Northern India. *Indian J Hematol Blood Transfus*, **27**, 93-5.

Ozkalemkas F, Ali R, Ozkocaman V, et al (2005). The bone marrow aspirate and biopsy in the diagnosis of unsuspected nonhematologic malignancy: a clinical study of 19 cases. *BMC Cancer*, **5**, 144.

Papac RJ (1994). Bone marrow metastases: a review. *Cancer*, **74**, 2403-13.

Paydas S, Ergin M, Baslamisli F, et al (2002). Bone marrow necrosis: clinicopathologic analysis of 20 cases and review of the literature. *Am J Hematol*, **70**, 300-5.

Ringenberg QS, Doll DC, Yarbro JW, Perry MC (1986). Tumors of unknown origin in the bone marrow. *Arch Intern Med*, **146**, 2027-8.

Sar R, Aydogdu I, Ozen S, Sevinc A, Buyukberber S (2001). Metastatic bone marrow tumours: a report of six cases and review of the literature. *Haematologia (Budap)*, **31**, 215-23.

Shah NT, Tuttle SE, Strobe1 SL, Gandhi L (1985). Prostatic carcinoma metastatic to bone: sensitivity and specificity of prostate-specific antigen and prostatic acid phosphatase in decalcified material. *J Surg Oncol*, **29**, 265-8.

Taiwan Health Registry Annual Report (2009). Bureau of Health Promotion, Department of Health, Executive Yuan, Republic of China. Available from: http://www2.cmu.edu.tw/~biostat/online/DOH1000602.pdf (Last accessed May 20 2013)

Trillet-Lenoir VN, Arpin D, Brune J (1994). Bone marrow metastases detection in small cell lung cancer. A review. *Anticancer Res*, **14**, 2795-7.

Tritz DB, Doll DC, Ringenberg QS, et al (1989). Bone marrow involvement in small cell lung cancer. *Cancer*, **63**, 763-6.

Wang JM, Shin LY, Lai GM, NG KT (1987). Bone marrow metastases from solid Tumors: clinical analysis of 96 cases. *Chang Gung Med J*, **10**, 283-93.

Wong KF, Chan JK, Ma SK (1993). Solid tumour with initial presentation in the bone marrow- a clinicopathologic study of 25 adult cases. *Hematol Oncol*, **11**, 35-42.

Xiao L, Luxi S, Ying T, et al (2009). Diagnosis of unknown nonhematological tumors by bone marrow biopsy: a retrospective analysis of 10,112 samples. *J Cancer Res Clin Oncol*, **135**, 687-93.