Metastatic Bone Marrow Tumors Manifested by Hematologic Disorders: Study of Thirty-Four Cases and Review of Literature

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Abstract: *Purpose*: Bone marrow metastasis of cancer is a sign of extensively hematogenous spreading of cancer and may be a terminal event of those patients. With the improvement of systemic chemotherapy for malignant disease, some patients may have longer survival. We plan to find out the clinical hematologic presentation and prognostic factors in cancer patients with bone marrow metastasis.

Materials & Methods: In this retrospective study, we reviewed the results of 162 bone marrow examination carried out in adult malignancy patients (colon, lung, gastric, breast and prostate cancers) between January 2002 and December 2012 in Changhua Christian Hospital. The indication for bone marrow study for those patients with hematologic disorders included: leukoerythroblastosis, microangiopathic hemolytic anemia, unknown etiology of anemia, thrombocytopenia, bicytopenia and pancytopenia. Statistics analysis used SPSS 18.0 and overall survival was analyzed with the use of Kaplan–Meier curves and the log-rank test.

Results: Thirty-four patients (20.9%) had evidence of involvement of the bone marrow by a solid tumor, most common cancers were prostate and lung. At the time of diagnosis, the most common hematologic disorders were leukoerythroblastosis and microangiopathic hemolytic anemia. Median survival after the diagnosis of bone marrow metastasis with supportive care only compared with definite treatments was 0.3 months and 20.6 months ($p<0.0001$). Patients with visceral organ metastasis (0.4 months vs 6.4 months, respectively; $p <0.002$) and anemia (2.1 months vs 6.4 months, $p=0.031$) had inferior survival. Patents without any cytopenia had better survival (12.5 months vs 4.1 months, $p=0.029$). Initial level of thrombocyte and neutrophil, bone marrow infiltration type (focal or diffuse) and disease status were not significant prognostic factor.

Conclusions: Visceral metastasis and anemia are most poor prognostic factors in solid cancers with bone marrow metastasis. Since the improvement of the diagnosis and treatment for cancers during the recent decades, a portion of patients can be had better disease control after definite treatment especially in breast and prostate cancers with bone marrow metastasis.

Keyword: Bone marrow metastasis, leukoerythroblastosis, microangiopathic hemolytic anemia, bone marrow involvement, adenocarcinoma.

INTRODUCTION

Cancer may spread to the bone marrow *via* the hematogenous route. In adult, prostate, breast, lung and gastric cancers are most seen in solid cancer with bone marrow involvement [1]. The cancer with bone marrow metastasis usually has the symptom of dizziness, bleeding and infection, resulted in morbidity and even mortality. The prognosis of these cases is dismal. Early diagnosis of bone marrow metastasis was depended on alert clinical clues, hematologic disorders included leukoerythroblastosis, disseminated intravascular coagulation or unexplained cytopenia, image study may use by such as magnetic resonance imaging, computed tomography, technetium-99m methyldiphosphonate (Tc-99m MDP) bone scintigraphy, and 18-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT). Bone marrow trephine biopsy gave the definite diagnosis [2]. However, the terminal event of concept of cancer with bone marrow metastasis may be changed due to advanced development in cancer treatment in the recent decades. In this retrospective study, we try to find out the clinical hematologic presentation and prognostic factors in patients with malignancy with bone marrow metastasis. We also explored the variably effect in relevant subgroups in our institution

METHODS

In this study, we reviewed the results of 162 bone marrow examination carried out in adult malignancy patients (colon, lung, gastric, breast and prostate cancer) between January 2002 and December 2012 in the division of Hematology and Oncology in Changhua Christian Hospital in Taiwan. All histopathologically proven malignancy with bone marrow metastasis were included in this study with written inform consent for

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trephine biopsy. We perform bone marrow biopsy from posterior iliac spine and sent for immunohistochemistry staining for each marker. The indication for bone marrow study for those patients with hematologic disorders included: leukoerythroblastosis, microangiopathic hemolytic anemia (MAHA), disseminated intravascular coagulation, unknown etiology of anemia, thrombocytopenia, bicytopenia and pancytopenia. If imaging study by computed tomography, magnetic resonance imaging or Tc-99m MDP bone scan revealed possible bone marrow metastasis in which bone marrow examination was also performed. Baseline clinical characteristics of patients including age, gender, physical status, presenting symptoms, disease status, visceral organ metastasis, hematologic disorders and biochemical parameters were also reviewed (anemia was defined as hemoglobin value ≤8.o mg/dL, thrombocytopenia as platelet count below 100,000/μL and leukopenia as white blood cell count lower than 3500/μL). Types of treatment (chemotherapy, radiotherapy, hormone and target therapy) and disease control rate (according to RECIST criteria version 1.1, disease control rate is sum of complete response, partial response and stable disease) were collected. The median survival was reviewed with all above possible prognostic factors.

STATISTICAL ANALYSIS

Statistics analysis used SPSS 18.0 and median overall survival was analyzed with the use of Kaplan–Meier curves and the log-rank test.

RESULTS

Between 2002 and 2012, bone marrow metastasis was found in 34 patients among 162 bone marrow examination in cancer patients: 13 patients were prostate cancer, 10 patients were lung cancer, 7 patients were breast, three patients were gastric and one patient was pancreas cancer. Patient's age range between 31 and 81 years (median age: 63). Seven patients were female. The histological subtype in 23 out of 34 patients was adenocarcinoma. 28 patients have focal bone marrow infiltration and six patients have diffuse bone marrow infiltration. Eight patients have visceral organ metastasis (5 patients in lung, one each of prostate, breast and gastric cancer). 20

Table 1: Clinical Characteristic of the Patients

	All patients (n=34)	Prostate cancer (n=13)	Lung cancer (n=10)	Breast cancer (n=7)	Others (n=4)
Age <65 y	16/34	1/13	5/10	7/7	3/4
Age>65 y/o	18/34	12/13	5/10	0/7	1/4
Male	27/34	13/13	10/10	7/7	0/4
Female	7/34	0/13	0/10	0/7	4/4
Performance					
0-2	22	10	4	5	3
3-4	12	3	6	2	1
Pathology					
adenocarcinoma	23/34	13/13	6/10	0/7	4/4
Others	11/34	0/13	4/10 (4 : smell call lung cancer)	7/7 (3: Infiltrating lobular carcinoma 4: infiltrating ductal carcinoma)	0/4
Visceral metastasis					
No metastasis	26	12	5	6	3
Yes	8	1	5	1	1
Lung		1	5	1	1
Liver		0	1	1	0
Others		0	0	0	0
Disease status					
Initial diagnosis	20	8	8	2	2
Relapse/refractory	14	5	2	5	2

patients were initial diagnosis of their malignant diseases with bone marrow metastasis and 14 patients were relapse/ refractory status. Clinical characteristics of these patients were summarized in Table **1**.

At the time of diagnosis, the most common hematologic disorders were: 13 patients were found to have leukoerythroblastosis, 13 patients were MAHA, one of each was unexplained pancytopenia, bicytopenia, isolated anemia or thrombocytopenia. There were five patients without hematological presentation received bone marrow examination due to image finding of suspicious bone marrow metastasis (Table **2**).

Table 2: The Hematological Parameter of our Patient in Study

Hematologic finding	N =34 (%)
MAHA+LEB	13 (38)
LEB	13 (38)
Pancytopenia	1 (3)
Bicytopenia	1 (3)
Isolated anemia or thrombocytopenia	1 (3)
No hematological finding (Image finding only)	5 (15)

MAHA: microangiopathic hemolytic anemia; LEB: leukoerythroblastosis.

Out of 34 patients, 24 patients received treatment (hormone, chemotherapy, radiotherapy or target therapy). 10 patients did not receive treatment due to poor performance (n=4), sepsis (n=2), old age (n=3), patient or family refuse (n=1). 17 patients got disease control as best response according to the evaluation of measurable lesions by primary attending physician at least three months after start specific treatments (14 patients has partial response, 3 patients has stable response) and 7 patients had progressive disease. Six patients with anemia got improvement or normalization of anemia after treatment. Five patients with thrombocytopenia and three patients with leukopenia got improvement or normalization. In MAHA subgroup (n=13), 6 patients were treated with hormone therapy (n=3) and chemotherapy (n=3), respectively. Three patients with hormone therapy in MAHA groups achieved normalization of blood count and others with cytotoxic agents did not have hematological response.

Median survival after the diagnosis of bone marrow metastasis, compared between supportive care only with definite treatment groups (radiotherapy, chemotherapy, hormone or target therapy) were 0.3 month and 20.6 months (p<0.0001) (Figure **1A**). The significance of survival benefit was also noted in subgroups of prostate cancer (0.16 month vs 12.6 months, p=0.001) and breast cancer (0.23 month vs 44.4 months, p= 0.008). In patients were treated with definite treatment subgroup, the median survival were 7.2 months in prostate cancer, 3.1months in lung cancer and 44.4 months in breast cancer. In patients did not have any cytopenia as initial presentation or only image disclosure group, because they have relatively preserved bone marrow function so that also have better survival (12.5 months vs 4.1 months, p=0.029). Compared median survival in patient with/ without visceral organ metastasis (0.4 month vs. 6.4 months, respectively; p =0.003) (Figure **1B**), w/o microangiopathic hemolytic anemia (2.1months vs 6.4 months, p=0.053), and w/o anemia (2.1 months vs 6.4 months, p=0.031) respectively (Figure **1C**). In patients received definite treatment subgroup, visceral organ metastasis still has inferior survival (3.0 months vs 29.0 months, p<0.001). Initial thrombocytopenia, neutropenia, bone marrow infiltration type (focal or diffuse) and disease status did not correlate with patient's outcome.

Table 3: The Treatment Outcome and Overall Survival in our Study

	All patients (n=34)	Prostate cancer (n=13)	Lung cancer (n=10)	Breast cancer (n=7)	Others (n=4)
Treatment (R/T, hormone therapy, C/T)					
Yes					
Disease control/ Total	17/24	10/12	1/5	5/5	½
Not	10	1	5	2	2
Median overall survival (days)					
Treatment					
Yes	619	216	93	1333	N
Not	10	5	10	7	
	P<0.0001	P=0.001	P=0.056	P=0.008	

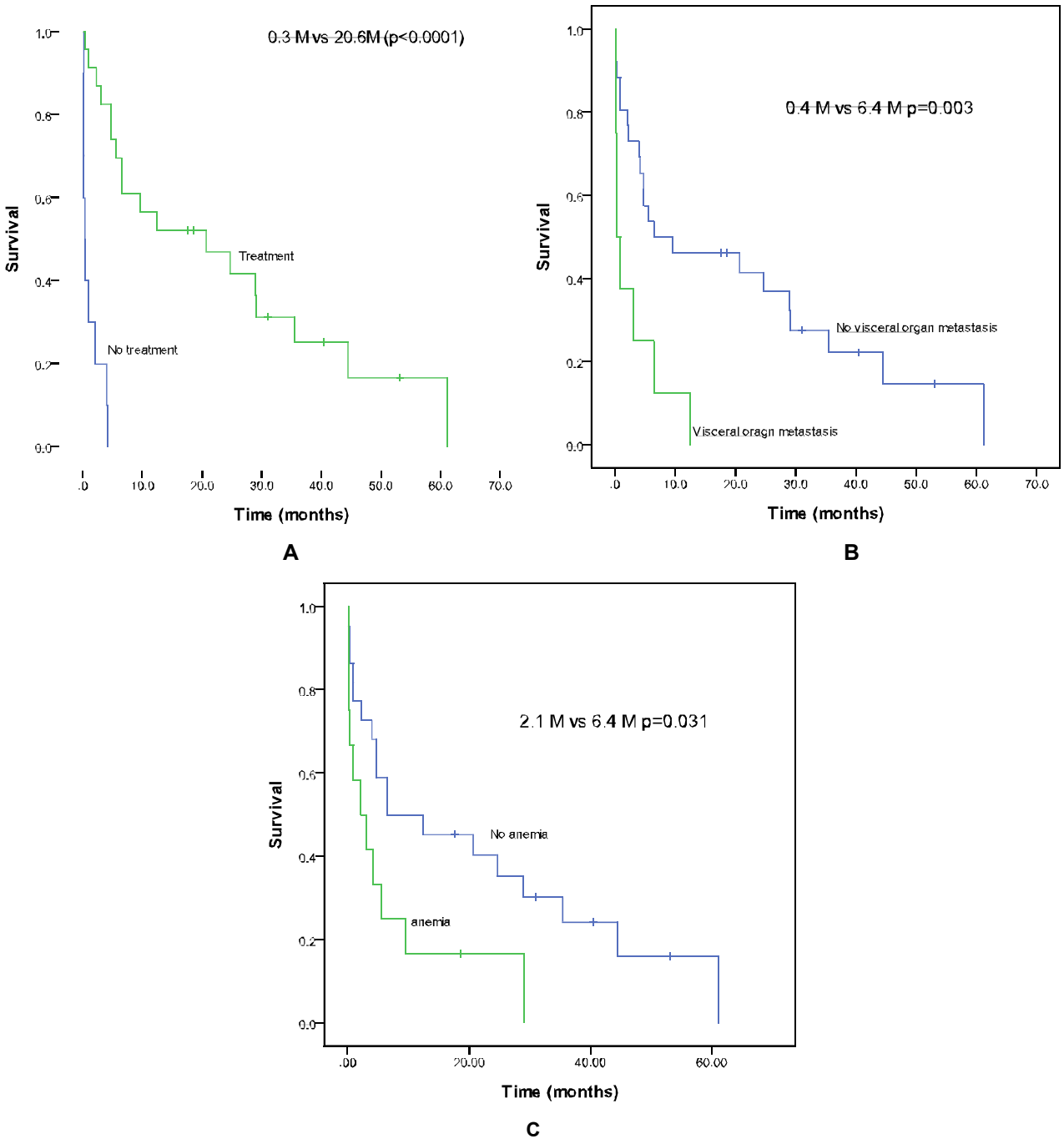

Figure 1: A: Kaplan-Meier survival curve showed the overall survival rates between patients had treatment or not.
B: Kaplan-Meier survival curve showed the overall survival rates between patients with or without visceral organ metastasis.
C: Kaplan-Meier survival curve showed the overall survival rates between patients with or without anemia.

DISCUSSION

Bone marrow metastasis had been reported in non-hematological malignancy, most including carcinoma of prostate, breast, lung and gastric and neuroblastoma [3-4]. This is a critical status, not only imply high tumor burden due to diffuse hematogenous spread but also increase risk of infection and bleeding, especially microangiopathic hemolytic anemia [5]. Some studies postulated these hematologic hints of bone marrow metastasis included leukoerythroblastosis, MAHA, leucopenia, unexplained cytopenia, raised serum alkaline phosphatase level, LDH or red cell distribution width. Our study also demonstrated the same findings as previous reports [6-8].

The prognostic significance of bone marrow metastasis also had been discussed in previous

literatures in breast cancer [9] and prostate cancer [10]. The detection of bone marrow metastasis possible is a critical issue for determined prognosis, help to design and control by new therapeutic strategies and minimal residual disease monitor [11].

In our study, patients with bone marrow metastasis and unable to receive definite treatment had very poor outcome with median survival of around 10 days only. In contrast, those patients receiving definite treatment had longer survival with median survival of 20.6 months and seventeen patients got disease control. The improvement of hematological presentation is affected by systemic chemotherapy or hormone therapy, which were used to eradicate cancer cells in bone marrow, thus restoring bone marrow function. Breast and prostate cancer subgroups still have relatively longer survival compared with other cancers. This finding could be explained by hormone therapy is main treatment for them and that did not result in further myelosuppresion compared with cytotoxic chemotherapy for other cancers. The relative poor survival in lung cancer may be related from less chance of disease control after treatment (20%) and more visceral organ metastasis in our patients. Our data support again the fact of diagnosis of bone marrow metastasis alone should not be regarded as a poor prognosis indicator, especially in breast and prostate cancer patients. The some result had been reported in the successful use of definite treatments resulted in bone marrow remission and have relatively longer survival [12-13]. Patents without any cytopenia had better survival (12.5 months vs 4.1 months, p=0.029), also is the group of patient need to be intensive treat.

Not all patients have visceral organ metastasis simultaneous during the diagnosis of bone marrow metastasis. In our study lung cancer is the most common one. In our analysis, visceral metastasis and anemia are most grave prognostic factors in solid cancers with bone marrow metastasis, which can be explained by vital organ damage and disseminated tumor condition. Also, in definite treatment group patients whom had visceral metastasis still had inferior survival than no-visceral group that means definite treatment cannot save every patient. Kopp *et al.* describe that their breast cancer patients had initial diagnosis with bone marrow metastasis, the median overall survival was 11 months [14]. Our breast cancer patients have longer median survival (44.4 months) than Kopp group, because they 50 % had visceral organ metastasis and we just only one patient (13%). These results repeatedly demonstrate visceral organ metastasis is a poor prognostic factor. Thrombocytopenia can add up to yield an overall worse prognosis was reported in one study [15]. However, initial LDH, thrombocytopenia or neutropenia did not found to correlate with survival rate in our study. The fear of cytopenic complications, such as febrile neutropenia or bleeding events, should not prevent to administering efficient combination chemotherapy for those patients.

Anemia could be result from MAHA, anemia of chronic disease, inadequate nutrition status or bone marrow reserve and bleeding event in cancer patients. Then, anemia is a poor prognostic factor in our study may be also multifactorial. In the beginning we propose that most resulted from MAHA but in the analysis it cannot reach the significance of survival, possibly due to smaller case number with MAHA in present study.

There was no significant survival benefit prefer focal or diffuse infiltration pattern also may be result from small case number. Bone marrow metastasis were found both in initial cancer diagnosis (n=20) and late developed (n=14). There were fourteen patients with relapse/ refractory status. These patients did not receive any systemic treatment at least one month before enrollment in our study. We considered that the initial hematological presentation was not affected by systemic chemotherapy. There was also no significant difference in survival (6.4 months vs 4.1months, p=.38). The same finding was reported in previous breast cancer study [14].

In conclusion, presence of leukoerythroblastosis, microangiopathic hemolytic anemia and unexplained cytopenia in cancer patients indicated the probable sign of bone marrow infiltration. Bone marrow trephine biopsy is a definite diagnostic tool to investigate bone marrow metastasis. Even the presence of bone marrow metastasis, it is not always means as a terminal event. Since the improvement of the diagnosis and treatment for cancers during the recent decades, a portion of patients can be had better disease control after definite treatment especially in breast and prostate cancers with bone marrow metastasis. However, visceral metastasis and anemia still are worse prognostic factors for them and prognosis of patients with bone marrow metastasis still is generally poor. In the future, development of more effective diagnostic and therapies strategies for those patients and larger study is warranted.

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We confirmed the Helsinki Declaration of 1975, as revised in 2000 concerning human and animal rights and that informed consent had been followed.

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