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Evaluation of Solid Tumor Patients Presenting with Denovo Bone Marrow Metastasis

Denovo Kemik İliği Metastazı ile Prezante Olan Solid Tümörlü Hastaların Değerlendirilmesi

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ABSTRACT

Aim: Although solid tumors are known to metastasize to the bone marrow, it is rare to be diagnosed with bone marrow involvement. In our study, we aimed to contribute to the literature by evaluating the treatment results and follow-up processes of different solid tumors metastatic to bone marrow in denovo.

Material and Methods: We retrospectively analyzed 28 patients who underwent bone marrow biopsy with a prediagnosis of hematologic malignancy and were diagnosed with carcinoma metastasis. Clinicopathologic features, antitumor treatments, treatment-related hematologic toxicities and factors affecting survival were evaluated.

Results: Of the 28 patients included in the study, 14 (50.0%) were female and 14 (50.0%) were male. The median age of the patients was 62 years (28-82). Eight patients (28.6%) were diagnosed with breast (28.6%), six with gastric (21.4%), four with lung (14.3%), two each with colon and prostate ca (7.1%), and the primary tumor site could not be determined in six patients (21.4%). Progression was observed in four (40.0%) of the 10 patients with the first series of treatment, three (30.0%) patients had stable response and three (30.0%) patients had partial response. The median progression-free survival time was 130 days (3-494 days) in patients who received first line treatment. The median overall survival time was 26 days (0-1183 days). Thrombocytopenia ($p<0.05$), hypofibrinogenemia ($p<0.05$), and poor performance score ($p<0.05$) were associated with lower survival.

Conclusion: Solid tumor patients diagnosed with denovo bone marrow metastases have a very poor prognosis. Additional poor prognostic factors in these patients include thrombocytopenia, hypofibrinogenemia, poor performance status. Accurate and rapid diagnosis of the primary solid tumor through bone marrow biopsy can help establish an appropriate treatment approach focused on the primary carcinoma.

Keywords: Bone marrow metastasis, solid tumors, toxicity

ÖZ

Amaç: Solid tümörlerin kemik iliği metastazı yaptığı bilinmesine rağmen kemik iliği tutulumu ile tanı almaları nadir görülmektedir. Çalışmamızda denovo kemik iliği metastatik farklı solid tümörlerin tedavi sonuçları ve takip süreçlerini değerlendirerek literatüre katkı sağlamak amaçlanmıştır.

Gereç ve Yöntemler: Hematolojik malignite ön tanısı ile kemik iliği biyopsisi yapılan ve karsinom metastazı tanısı alan 28 hasta retrospektif olarak incelendi. Hastaların klinikopatolojik özellikleri, aldıkları antitümör tedaviler, tedavi ilişkili hematolojik toksisiteleri ve sağkalımlarına etki eden faktörler değerlendirildi.

Bulgular: Çalışmaya dahil edilen 28 hastanın 14'ü (%50,0) kadın, 14'ü (%50,0) erkekti. Hastaların median yaşı 62 (28-82) idi. Hastaların sekizi (%28,6) meme, altısı mide (%21,4), dördü akciğer (%14,3), ikişer (%7,1) tanesi de kolon ve prostat ca (%7,1) tanısı almış olup altı hastanın (%21,4) primer tümör bölgesi belirlenememiştir. Tedavi verilen 10 hastanın dört tanesinde (%40,0) ilk seri tedavi ile progresyon gözlenmiş olup, üç hastada (%30,0) stabil, üç (%30,0) hastada parsiyel tedavi yanıtı elde edilmiştir. İlk seri tedavi alan hastalarda progresyonsuz sağkalım süresi median 130 gün (3-494 gün) gözlenmiştir. Hastaların median genel sağkalım süresi 26 gündür (0-1183 gün). Trombositopeni ($p<0,05$), hipofibrinojenemi ($p<0,05$) ve kötü performans skoru ($p<0,05$) daha düşük sağkalımla ilişkili bulunmuştur.

Sonuç: Denovo kemik iliği metastazı ile tanı alan solid tümor hastalarının prognozu çok kötüdür. Bu hastalardaki ek kötü prognostik faktörler arasında trombositopeni, hipofibrinojenemi, kötü performans durumu sayılabilir. Kemik iliği biyopsisi yoluyla primer solid tümörün doğru ve hızlı teşhisi ile primer karsinom üzerine odaklanan uygun bir tedavi yaklaşımının oluşturulmasına yardımcı olabilir.

Anahtar Sözcükler: Kemik iliği metastazı, solid tümörler, toksisite

INTRODUCTION

Although bone marrow (BM) involvement is frequently observed in haematological malignancies, bone marrow metastases of solid organ malignancies are rare (1,2). BM metastases are diagnosed in 0.2%-12% patients with solid malignancies. In adults, BM metastases of breast, lung and prostate cancers are observed most frequently after lymphomas (3). However, it is even rarer for patients without a diagnosis of malignancy to be diagnosed with BM metastasis. The cancer with BM metastasis usually has the symptom of dizziness, bleeding and infection, resulted in morbidity and even mortality. The prognosis of these cases is poor. Early diagnosis of BM 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 (18F-FDG PET/CT) (4). These patients are mostly diagnosed in haematology clinics after BM biopsy evaluations as a result of cytopaenia-induced investigations. In our study, it was planned to evaluate the clinicopathological characteristics of solid tumour patients with BM metastasis, whose follow-up and treatment processes are challenging in medical oncology practice and whose treatment protocols are unclear due to the lack of randomised studies, and the contribution of treatment protocols to the survival of patients and treatment-related haemotological toxicities. When the literature is reviewed, there are limited number of studies evaluating the diagnosis and treatment processes of denovo BM metastatic patients, and the majority of these studies are in the form of case reports or evaluation of bone marrow metastases of a specific solid tumour. We aimed to contribute to the literature by evaluating the treatment results and follow-up processes of different solid tumours with denovo BM metastasis.

MATERIAL and METHODS

Local ethics committee approval (Date: 15.02.2022 decision no: 32, Number: E-25403353-050.99-305318) was obtained before the study, which was planned as a retrospective cohort study, and the Helsinki Declaration criteria were taken into consideration. The records of patients with BM carcinoma metastases detected in BM biopsies evaluated by the Pathology Department of Eskisehir Osmangazi University Faculty of Medicine Hospital between 2011 and 2021 were retrospectively reviewed. Among the patients with bone marrow metastases, 28 patients who were 18 years of age or older, had haemogram and coagulation tests performed before biopsy, and had no previous diagnosis of solid organ cancer or haematological cancer were included in the study. Gender, age at diagnosis, date of diagnosis, primary tumour site if detected, pathological subtype, other metastasis sites, hematological and coagulation parameters (haemoglobin (Hb), platelet, leukocyte, lymphocyte, fibrinogen, D-Dimer, activated partial thromboplastin time, international normalized ratio), lactate dehydrogenase, tumour markers , whether the patient received treatment for cancer diagnosis, if chemotherapy or hormonotherapy treatment was received, start and end times of treatment, maximal response to treatment (according to RECIST criteria version 1.1) (5), last visit or death dates of the patients were recorded and evaluated. Hb<13 g/dL in men and Hb<12 g/dL in women were considered as anaemia. Leukocyte count<4000/mm^3 was considered as leukopenia, neutrophil count<1500/mm^3 as neutropenia and platelet count<100.000/mm^3 as thrombocytopenia (6).

Statistical Analysis

Mean, standard deviation, median, minimum, maximum values were given in descriptive statistics related to continuous data, and number and percentage values were given in discrete data. Shapiro-Wilk test was used to examine the conformity of continuous data to normal distribution. Chi-Square/Fisher's Exact test was used for group comparisons

of nominal variables (cross tabulations). Kaplan-Meier survival analysis and log rank method were used to analyse the differences in survival between independent groups. In addition, Cox regression analysis method was used to determine the factors affecting survival. IBM Statistical Package for the Social Science Statistics for Windows version 20 (Chicago, IL, USA) was used in the evaluations and $p<0.05$ was accepted as the statistical significance limit.

RESULTS

Of the 28 patients included in the study, 14 (50.0%) were female and 14 (50.0%) were male. The median age of the patients was 62 years (28-82). All patients underwent bone marrow biopsy after referral to the haematology department. 15 patients (53.6%) were diagnosed as adenocarcinoma, four patients (14.3%) were diagnosed as neuroendocrine carcinoma, and nine patients (32.1%) had pathological examination as carcinoma metastasis with undetermined subtype. Eight (28.6%) patients were diagnosed with breast, six (21.4%) with stomach, four (14.3%) with lung, 2 (7.1%) each two with colon and prostate ca (7.1%), and the primary tumour site of six (21.4%) patients could not be determined (Table 1). Baseline laboratory parameters of the patients are summarised in Table 2. The most common reasons for bone marrow biopsy were bicytopenia (28.6%), pancytopenia (25.0%), and multiple myeloma (17.9%), respectively. The most common site of metastasis accompanying bone marrow metastasis were bone metastasis (90.4%), lymph node metastasis (89.3%), visceral metastasis (50.0%), brain metastasis (7.1%), skin metastasis (3.5%). After the diagnosis, 10 of the patients could receive oncological treatment, one patient was lost to follow-up and 17 patients died without receiving treatment. The first-line treatment regimens and side effects observed are summarised in Table 3. Progression was observed in four (40.0%) of 10 patients who received treatment with the first series of treatment, three (30.0%) patients were stable and three (30.0%) patients had partial treatment response. Progression-free survival (pfs) median 130 days (3-494 days) was observed in patients who received the first series of treatment. The second series of treatment could be started in five patients with treatment response. The median overall survival (OS) was 26 days (0-1183 days). Longer pfs and OS times were

Table 1: Clinical characteristic of the patients.

Parameters	Findings (n= 28)	
Age, year [median (min-max)]	62	(28-82)
Gender*		
Female	14	(50.0)
Male	14	(50.0)
Pathological diagnosis*		
Breast cancer	8	(28.6)
Gastric cancer	6	(21.4)
Lung cancer	4	(14.4)
Colorectal cancer	2	(7.1)
Prostate cancer	2	(7.1)
Primary unknown	6	(21.4)
Pathological subtype*		
Adenocarcinoma	15	(53.6)
Neuroendocrine carcinoma	4	(14.3)
Carcinoma metastasis of undetermined subtype	9	(32.1)
Eastern Cooperative Oncology Group Performance Score*		
ECOG 1	0	(0.0)
ECOG 2	10	(35.7)
ECOG 3	8	(28.6)
ECOG 4	10	(35.7)

*Data are presented as n (%). **ECOG**: Eastern Cooperative Oncology Group

Table 2: Baseline laboratory values.

Laboratory parameters*	Values (n=28)		
Haemoglobin (g/dl)	8.6±2.40	8.2	(4.0-14.6)
Platelet (10^3/µL)	104.000±1668.49	44.000	(5.000-770.000)
Absolute neutrophil count (10^3/µL)	6.05±5.81	3.6	(0.4-2.4)
Absolute lymphocyte count (10^3/µL)	1.4±0.7	1.4	(0.5-3.5)
Total leukocyte count (10^3/µL)	8.3±6.6	6.3	(1.1-2.8)
Fibrinogen (mg)	379.0±213.94	353.0	(102.0-821.0)
D-dimer (mg/L)	17.0±1.7	15.0	(2.0-44.0)
LDH (U/L)	1255.00±1084.0	716.0	(258.0-4236.0)
CEA (ng/mL)	58±66.4	42	(1.05-228)

*Data are presented as mean±standart deviation and median (minimum-maxiumum).
SD: Standart deviation, **LDH:** Lactate dehydrogenase, **CEA:** Carcino-embryogenic antigen

Table 3: Summary of cases given first-line treatment.

Patient No	Age Gender	First-line treatment	Pathological diagnosis	Cytopenia before treatment	Maximum response to treatment	Pfs (day)	Os (day)	Toxicity
1	59/M	Cisplatin -Etoposide	Colon neuroendocrine carcinoma	Bi-cytopenia	Partial	201	301	No (raised platelets)
2	48/M	Carboplatin -Paclitaxel	Lung neuroendocrine carcinoma	Bi-cytopenia	Progression	13	33	No
3	43/F	Carboplatin -Paclitaxel	Breast adenocarcinoma	Pan-cytopenia	Stable	60	191	No (raised platelets)
4	28/F	Cisplatin	Gastric adenocarcinoma	Bi-cytopenia	Progression	3	17	No
5	54/F	Carboplatin	Primary unknown	Pan-cytopenia	Progression	18	26	Yes
6	44/F	Docetaksel -Capesitabine	Breat adenocarcinoma	Anemia	Stable	344	479	No
7	60/M	Fluorourasil	Gastric adenocarcinoma	Bi-cytopenia	Progression	16	27	No (raised platelets)
8	43/F	Tamoxifen	Breast adenocarcinoma	Anemia	Partial	494	1183	No
9	59/F	Letrozole	Breast adenocarcinoma	Bi-cytopenia	Partial	294	536	No
10	76/M	Enzalutamide	Prostate adenocarcinoma	Anemia	Stable	360	401	No

Pfs: Progression free survival, **Os:** Overall survival.

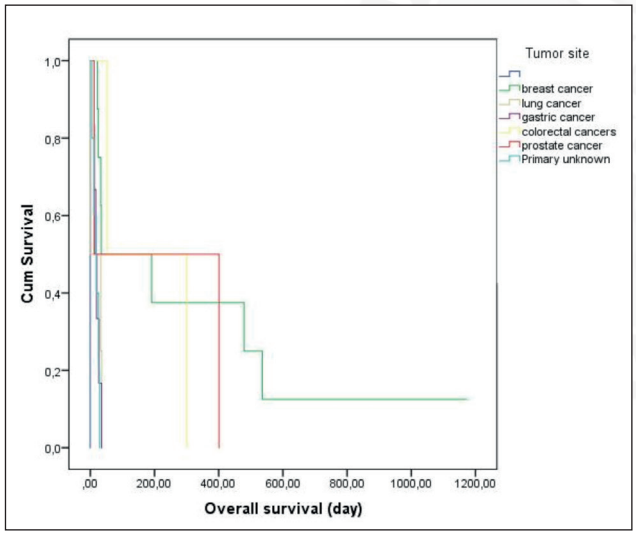

Figure 1: Effect of tumor subtypes on overall survival.

observed in breast cancer and prostate cancer diagnoses (Figure 1). Thrombocytopenia ($p<0.05$) and hypofibrinogenemia ($p<0.05$) were associated with lower survival (Figure 2A,B).

DISCUSSION

BM evaluation is the most useful and sensitive technique to detect BM metastases in non-haematological malignancies. Infiltration of bone marrow by solid tumours is an important presentation. However, denovo BM metastasis of solid tumours is a rare entity. These patients were not enrolled in clinical trials because of advanced stage, poor performance status, or abnormal laboratory results. Therefore, the clinical features and prognostic factors of these patients remain an issue. In our study, we think that we have contributed to the literature by presenting the data of 28 denovo metastatic patients. Agrawal et al. reported that 22 of 1538 bone marrow biopsies (1.4%) showed bone marrow infiltration by solid tumours. Ten of these solid tumour infiltrations represented denovo metastatic solid tumour patients (7). In the study of Kilickap et al. in which 3842 bone marrow biopsy materials were evaluated, the rate of total solid organ metastasis to the bone marrow was found to be 1.9% (8). In the study by Zhou et al. 14 of 30 patients with bone marrow metastasis were denovo metastatic disease (9). As can be seen, there is no multicenter study with a large number of patients in the literature and the number of patients in single-center studies is limited.

Patients with bone marrow metastases have a poor prognosis due to rapid disease progression and poor response to treatment (10,11). The prognostic features of patients with bone marrow metastasis include primary tumor site, performance status, platelet count and therapeutic regimens (12). The most common malignancies metastasizing to the bone marrow in the adult population have been reported as gastric, prostate and breast cancers in different studies (2,13). There is no comprehensive study evaluating tumor subtypes in solid malignancies diagnosed with bone marrow metastasis. Breast cancer is one of the most common tumors metastasizing to the bone marrow. However, the diagnosis of breast cancer from bone marrow is very

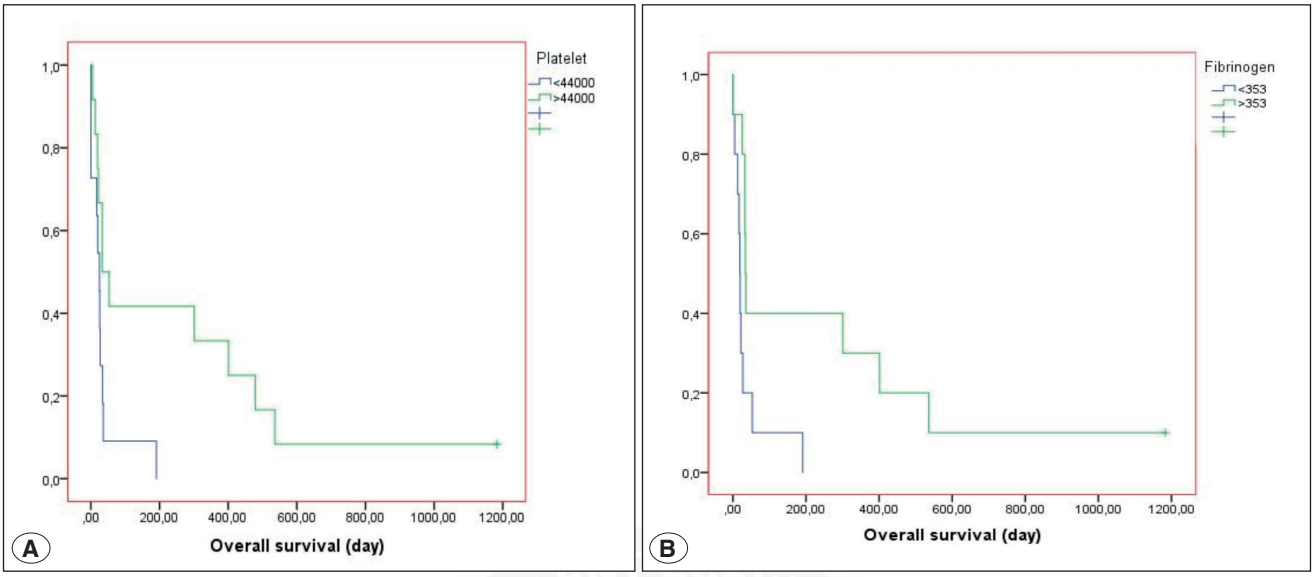

Figure 2: Impact of thrombocytopenia **(A)** and hypofibrinogenemia **(B)** on overall survival.

rare. Only 0.17% can be detected (14). There is no standard treatment regimen recommendation and the majority of patients in this group are followed up with supportive care. It can be challenging for clinicians to choose between systemic antitumor therapy or supportive treatment. In our patient group, 17 patients (60.7%) died before receiving systemic therapy due to poor performance status. It has been observed that antihormone therapy contributed to progression-free survival in patients with breast cancer, the most common tumor subtype in our population. There are also case reports showing that the use of targeted antihormone therapy cyclin-dependent kinase (CDK) 4/6 inhibitors is safe and effective in patients with bone marrow metastatic breast cancer (15). One of our patients used antihormone and CDK 4/6 inhibitors as 2nd line therapy and no significant hematologic toxicity was observed during treatment. The possibility of additional hematologic toxicity that may develop with antitumor therapy in this patient group raises concerns among clinicians. Our study shows that the risk of additional hematologic toxicity decreases as a result of improvement in bone marrow function with treatment. Although prostate cancer is a tumor that frequently metastasizes to the bone marrow during its clinical course, its presentation with bone marrow metastasis is rare. As in breast cancer, patients with denovo bone marrow metastatic prostate cancer have been observed to benefit from antihormone therapy with a low risk of toxicity (16). In our study group, patients diagnosed with breast (312 days) and prostate cancer (206 days), respectively, had longer overall survival times, whereas the median survival time of the group of patients with unknown primary cancer was considerably shorter (18 days). 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.

In our study, thrombocytopenia was found to be a poor prognostic factor in correlation with literature data (17,18). Other poor prognostic factors were hypofibrinogenemia and poor performance status. Severely decreased platelet counts and fibrinogen levels are thought to increase the incidence of fatal bleeding complications in patients. In addition, the decision to start antitumor therapy in this patient group is difficult. In our study group, hypofibrinogenemia was more common in patients with stony ring cell adenocarcinoma and carcinoma of unknown primary metastases, and the majority of patients in this group had no chance to receive treatment due to poor performance status.

Since the diagnosis of solid tumors with denovo BM metastases is a rare entity, there are limited studies in the literature. We believe that it is important to plan multicenter studies with a larger number of patients in order to guide the follow-up and treatment of these patients.

In conclusion, the prognosis of solid tumor patients with denovo bone marrow metastases is very poor. Additional poor prognostic factors in these patients include thrombocytopenia, hypofibrinogenemia, poor performance status. Accurate and rapid diagnosis of the primary solid tumor through bone marrow biopsy can prevent the need for additional invasive procedures, ultimately helping to establish an appropriate treatment approach focused on the potentially curable and primary carcinoma.

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Author Contributions

Idea and design: **Duygu Bayir Garbioglu, Bulent Yildiz,** Data and literature review: **Duygu Bayir Garbioglu, Serap Isiksoy, Nazan Demir, Murat Dincer,** Analysis and Comment: **Duygu Bayir Garbioglu, Bulent Yildiz, Murat Dincer,** Article writing: **Duygu Bayir Garbioglu, Nazan Demir.**

Conflicts of Interest

The authors of this article declare no conflicts of interest. This article is presented at 5th congress on an oncology perspective with young people. Online, 04-06 March 2022.

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Ethical Approval

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