RESEARCH ARTICLE

Cisplatin Plus Gemcitabine for Treatment of Breast Cancer Patients with Brain Metastases; a Preferential Option for Triple Negative Patients?

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Abstract

Background: To assess the efficacy and tolerability of Cisplatin plus Gemcitabine combination in patients with brain metastases (BM) from breast cancer (BC). Materials and Methods: Eighteen BC patients with BM who were treated with Cisplatin plus Gemcitabine regimen between 2003-2011 were evaluated. Results: A median of 6 cycles of this regimen were received, in fifteen patients (83.3%) as first-line chemotherapy, in 2 as second-line and in 1 as third-line after diagnosis of BM. Dose reduction was performed in 11 (61.1%) patients; major reasons were neutropenia and leukopenia. Grade III neutropenia and Grade II trombocytopenia rates were 33.3% and 16.7% respectively. Overall response rate (ORR; complete+partial response rate) was 33.4% (n=6) for the entire study population; triple negative patients achieved an 66.6% ORR while hormone receptor (HR) positive patients had 25% and HER2 positive patients 12.5%. Median progression-free survival was 5.6 months (2.4-8.8 months, 95%CI) and longer in patients with triple negative breast cancer (TNBC) (median 7.4 months, 95%CI, 2.4-12.3 months) than the patients with other subtypes (median 5 months for HER2 positive and 3.6 months for HR positive patients). Median PFS of the patients with TNBC who received this regimen as first-line was 9.2 months (5.2-13.2 months, 95%CI). Conclusions: Cisplatin plus Gemcitabine may be a treatment option for patients with BM from breast cancer. Longer PFS and higher response rates are results that support the usage of this regimen especially for the triple negative subtype. However, further prospective and randomized trials are clearly required to provide more exact information.

Keywords: Breast cancer - brain metastases - cisplatin plus gemcitabine - triple negative

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Introduction

Breast cancer is the second most common cause of brain metastases, approximately, 10-16% of the metastatic breast cancer patients develop BM. The survival time of the BC patients shorten rapidly after the development of BM. Whole brain radiotherapy is a standart therapy given to all patients with central nervous system (CNS) involvement. Metastasectomy and stereotactic radiosurgery are the other therapeutic options for selective cases. Several retrospective studies demonstrated that systemic therapy after BM prolongs survival compared with only radiation therapy or best supportive care (Park et al., 2009; Niwinska et al., 2010; Kim et al., 2012). However, it is still not clear which therapy option is most effective.

Among breast cancer subtypes, HER2 positive patients usually have longer survival times compared to the patients with triple negative or luminal A subtypes due to the usage of new therapeutic anti-target agents in the last decade (Nam et al., 2008; Niwinska et al., 2010; Kim et al., 2012). Cisplatin is a DNA cross-linking agent and it has marked activity in various solid tumors. Objective response rates ranging from 42% to 54% were reported for Cisplatin as first-line single agent in metastatic breast cancer (Kolaric et al., 1983; Sledge et al., 1988), while response rates decrease to 0-9% in previously treated metastatic breast cancer patients (Ostrow et al., 1980; Forastiere et al., 1982). Gemcitabine is a chemotherapeutic agent that acts as a pyrimidine nucleoside antimetabolite, which has relatively low toxicity and as a single agent it achieves 14-37% of response rates (RR) as first-line and approximately 25% RR as salvage therapy (Carmichael et al., 1995; Brodowicz et al., 2000; Spielmann et al., 2001; Valerio et al., 2001). The combination of Cisplatin and Gemcitabine was investigated in several studies on patients with metastatic breast cancer (MBC); and 26-

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63% of RR were shown in those studies (Doroshow et al., 2000; Galvez et al., 2000; Nagourney et al., 2000; Heinemann et al., 2002; 2006; Somali et al., 2009). Herein, we investigated the efficacy of Cisplatin-Gemcitabine combination therapy in a subset of breast cancer patients with BM.

Materials and Methods

Patients

We retrospectively evaluated 18 patients who were diagnosed with BM due to breast cancer between 2003-2011 at a single center (Izmir Katip Celebi University, Ataturk Training and Research Hospital, Department of Medical Oncology) and were treated with Cisplatin plus Gemcitabine regimen at any line after BM. We carefully examined the medical records and histopathological data of these patients. The diagnosis of brain metastases was performed frequently by using magnetic resonance imaging (MRI) or computed tomography (CT). The performance status at time of the brain metastases was indivually recorded using the Eastern Cooperative Oncology Group (ECOG) scale (Oken et al., 1982). The stage was recorded by using TNM staging system (AJCC 7th edition, 2010; Cancer staging manual AJCC, 2010). Tumor differentiation or histologic grade was evaluated by Nottingham combined histologic grading system (Elston and Ellis, 1991; Fitzgibbons et al., 2000) which determines grade by assessing morphologic feature (tubule formation, nuclear pleomorphism, and mitotic count) and classifies as grade I-III (low grade, intermediate, or high grade).

Median ages at initial BC and BM diagnosis were 46 years (37-64 years) and 49 years (ranging between 37-66 years) respectively. The tumor histology was compatible with invasive ductal carcinoma in 15 patients (83.3%), invasive lobular in one patient (5.6%) and medullary in two patients (11.1%) (Table 1). Three patients (16.7%) had stage IV disease while 12 patients (66.6%) had stage III disease and 3 patients (16.7%) had stage II disease at initial BC diagnosis. The adjuvant treatment history of the patients with early BC at initial diagnosis are given in Table 2. The majority of these 18 patients had the history of receipt of anthracyclines or taxanes either in adjuvant or metastatic setting.

Median time to development of BM (TTBM) was 31.6 months (range: 7.47-128.5 months) in the study group. Eleven patients had good ECOG performance score (ECOG 0-1) at the time of BM diagnosis. Five patients had ECOG 2 and two patients had ECOG 3 performance score (Table 3). Six patients (33.3%) had solitary parenchymal lesion, three patients (16.7%) had 2 parenchymal lesions and 9 (50%) had multiple lesions. Seven patients had undergone metastasectomy operation of which 6 of them were performed for palliative aim. Only one patient had brain only metastasis and she underwent curative metastasectomy. All of the patients in the study group had received whole brain radiotherapy (WBRT) after diagnosis of BM whether they had undergone metastasectomy or not. Three patients in the study group had only brain metastases, while 15 patients had also extracranial metastases. The leading extracranial metastatic site was lung (8/18).

Table 1. Characteristics of the Patients at Initial Breast Cancer Diagnosis

Variable		N	%
Age	≤50	13	72.2
	>50	5	27.8
Stage	IIA	3	16.7
	IIIA	5	27.7
	IIIB	3	16.7
	IIIC	4	22.2
	IV	3	16.7
Menopausal status	Premenopausal	14	77.8
	Postmenopausal	4	22.2
ECOG at diagnosis	0-1	17	94.4
	2	1	5.6
Histologic type	IDBC	15	83.3
	ILBC	1	5.6
	MBC	2	11.1
Histologic grade	I	0	0
	II	9	50
	III	9	50
ER status	(+)	3	16.7
	(-)	15	83.3
PR G	(+)	5	33.3
	(-)	12	66.7
CERBB2	(-)	10	55.6
	(+)	8	44.4
Breast cancer fenotype	HR(-)HER2(-)	6	33.3
	HR(-)HER2(+)	6	33.3
	HR(+)HER2(-)	4	22.2
	HR(+)HER2(+)	2	11.1

*IDBC: Invasive ductal breast cancer, ILBC: Invasive lobular breast cancer, MBC: Medullary breast cancer

Table 2. Treatment Procedure of the Patients with Early Stage At Initial

Treatment procedure		N	%
Adjuvant chemotherapy	TEC	3	17.6
	FEC	3	17.6
	4EC-→4T	2	11.8
	4AC-→4P(dose dense)	2	11.8
	FNP	2	11.8
	CMF	1	5.9
Adjuvan radiotherapy	Yes	13	72.2
	No	5	27.8
Adjuvant endocrine therapy	Yes	3	16.7
	No	15	83.3
Operation procedure	Radical mastectomy+AD	13	72.2
	BCS+AD	2	11.1
	No	3	16.7

*EC: Epirubicine-Cyclophosphamide; FEC: 5FU-Epirubicin-Cyclophosphamide; T: Docetaxel, TEC: Docetaxel-Epirubicine-Cyclophosphamide; AC:Doxorubicine-Cyclophosphamide, P: Paclitaxel; FNP: 5FU-Vinorelbine-Cisplatin; CMF: Cyclophosphamide-Methotrexate-5FU; BCS: Breast conserving surgery, AD: Axillary dissection

Pathological data of the study population was also examined. Hormon receptor (HR) and human epidermal growth receptor-2 (HER2) status were determined by immunohistochemical (IHC) analysis. Immunohistochemical membranous 3 positivity of cerbB2 was accepted as HER2 positive, membranous 1+ or negative cases were defined as HER2 negative. Immunohistochemically cerbB2 (++) tissues were reevaluated by FİSH analysis; HER2 gene amplification greater than 2 was accepted as HER2 positive. The

following tumor subtypes were defined according to HR and HER2 status: i) HR positive, HER2 negative (known as Luminal A subtype), ii) HR positive, HER2 positive (known as Luminal B subtype), iii) HR negative, HER2 negative (triple negative), iv) HR negative, HER2 positive (HER2 enriched). Fifteen patients in the study group had ER(-), 12 patients had PR(-) disease. Twelve patients were immunohisohemically ER(-)PR(-), 3 patients were ER(-) PR(+), 2 patients were ER(+)PR(+). Eight patients (one of them by FİSH analysis) were HER2/neu positive. When we classified the patients according to the breast cancer subtypes by using immunohistochemical characteristics, 6 patients were HR(-)HER2(-) [or Triple negative], 6 patients were HR(-)HER2(+), 4 patients were HR(+) HER2(-) and 2 patients were HR(+)HER2(+) (Table 1).

Treatment procedure and response evaluation

Chemotherapy was performed according to following schedule: Cisplatin 30 mg/m^2 days 1 and 8, Gemcitabine 1000 mg/m^2 days 1and 8 in each a 21-day cycle. Due to the heavily-treated and metastatic nature of these patients, G-CSF prophylaxis was administered for 3 days 48 hours after day 1 and for 2 days after 48 hours following day 8. The toxicities experienced during treatment were graded according to WHO toxicity criteria (World Health Organization, 1979). Objective tumor responses were evaluated using WHO criteria (Miller et al., 1981). PFS was defined as the time from initiation of Cisplatin-Gemcitabine combination to the time for the progression or death or last visit which came first.

Statistical analysis

SPSS 16.0 (Statistical Package for the Social Sciences, version 16) programme was used to perform the statistical analysis. The means and medians of the variables were calculated by descriptive analysis. Categorical variables were compared using the Chi-square and Fisher's exact test. Kaplan-Meier analysis was used for survival analysis; the survival difference between subgroups were compared by Log-rank test. A two-sided p value of <0.05 was considered to be statistically significant.

Results

Patient characteristics

Fifteen patients (83.3%) received this chemotherapy regimen as first-line systemic therapy after WBRT. Among 15 patients, one patient had only solitary brain metastasis and received this regimen as adjuvant therapy after curative metastasectomy for 6 months, other 14 patients received this regimen until disease progression. Two patients (11.1%) received as second-line systemic therapy and one patient (5.6%) as third-line after BM.

Brain was the first recurrence site in 6 of these 18 patients (33.3%) (Table 3). Cisplatin-Gemcitabine combination was delivered as first-line therapy in 5 of these 6 patients. Among these 5 patients, 2 patients had TNBC at initial diagnosis and other two patients had history of metastasectomy whose metastatic tumor histology was compatible with triple negative fenotype. Cisplatin-Gemcitabine regimen was chosen as first-line therapy for these cases due to the triple negative nature of the primary tumor or metastatic lesion. One patient in this group received this regimen as second-line regimen after progressive response to taxane (single agent Docetaxel 100 mg/m^2) in the first-line regimen.

Twelve patients (66.7%) in the study group had developed metastases in other sites than brain as first recurrence site (Table 3 and 4). 10/12 patients were treated with this regimen for the first-line systemic therapy after BM. One patient received Cisplatin-Gemcitabine combination as second-line regimen after progression with single agent Docetaxel 100 mg/m^2 and another patient receieved this regimen as third-line regimen after BM after failure with Lapatinib-Capecitabine combination and Paclitaxel (80 mg/m^2-weekly). Among these 12 patients, three of them were metastatic at initial BC diagnosis. The treatment history of these patients before Cisplatin-Gemcitabine regimen are given in Table 4.

Toxicity

Median 6 cycles of this regimen were received. Dose reduction was performed in 11 (61.1%) patients. Median

Table 3. Characteristics of the Patients at the Time of Brain Metastases

Variable		N	%
Age at BM	<50	11	61.1
	≥50	7	38.9
First metastasis to brain	Yes	6	33.3
	No	12	66.7
First recurrence site	Bone/soft tissue/skin	8	44.5
	Lung and/or liver	4	22.2
	Brain	6	33.3
ECOG at BM	0-1	11	61.1
	2	5	27.8
	3	2	11.1
Type of CNS involvement	Parenchymal	17	94.4
	Parenchymal+leptomeningeal	1	5.6
Metastasectomy	Yes	7	38.9
	No	11	61.1
WBRT	Yes	18	100
	No	0	0
Cyberknife after WBRT	Yes	1	5.6
	No	17	94.4

Table 4. Treatment History of the Patients with First Recurrence Site Other Than Brain

Patients	First Recurrence Site	TTBM (months)	Breast Cancer Subtype	Ct Lines Before C-G	Received Ct Regimen
1	Lymph node-bone	40,4	HR(-)HER2(+)	1	Docetaxel+Trastuzumab
2*	Liver-lung-bone	37,2	HR(+)HER2(+)	2	FEC/Trastuzumab+Capecitabine
3	Lung	39,3	HR(-)HER2(+)	1	Docetaxel+Trastuzumab
4	Bone	17,3	HR(-)HER2(+)	1	Docetaxel+Trastuzumab
5	Bone	26,3	HR(-)HER2(-)	1	Docetaxel
6	Bone	128	HR(-)HER2(-)	1	Docetaxel
7*	Bone	21	HR(-)HER2(-)	2	FEC/ Docetaxel
8	Lymph node-bone	88,5	HR(+)HER2(+)	3	Docetaxel+Trastuzumab/ Lapatinib+Capecitabine/ Paclitaxel-weekly
9	Lymph node-skin-bone- bone marrow	47,5	HR(-)HER2(+)	1	Vinorelbine+Trastuzumab
10*	Lung	24,3	HR(-)HER2(-)	1	TAC followed by Docetaxel
11	Bone	49	HR(-)HER2(+)	1	Docetaxel+Trastuzumab
12	Bone	83	HR(+)HER2(-)	1	Docetaxel+Trastuzumab

*Means: the patients who were metastatic at initial BC diagnosis

total Cisplatin dosage received per patient was 355 mg (63.8% of planned cisplatin dose) and median Gemcitabine dose received per patient was 16600 mg (82.1% of planned dose). Grade III and IV neutropenia was observed in 4 (22.1%) and 2 patients (11.1%) respectively, however neutropenic sepsis were not seen in any of the patients. Grade I-II trombocytopenia were seen in 5 patients (27.7%). Severe trombocytopenia was observed only in one patient (5.6%), six patients (33.3%) developed grade I peripheral neuropathy during chemotherapy, however severe neuropathy was not seen. Grade I nephrotoxicity was observed in one patient (5.6%); chemotherapy was continued by Carboplatin instead of Cisplatin in this patient. Mild (grade I) hepatotoxicity was recorded in 4 patients (22.2%). Two patients experienced ototoxicity after third cycle and chemotherapy was continued by single agent Gemcitabine in these two patients (The toxicity profile is summarized in Table 5).

Efficacy

Overall response (complete+partial response) rate was 33.4% (n=6). Complete response was achieved in one patient (5.6%). Five patients (27.8%) had partial response, 8 patients had stable response (44.1%) and 4 patients (22.2%) had progressive disease. The objective response rate in patients with TNBC was 66.6% (4/6) while patients with other subtypes had a totally 16.6% of objective response rate (2/12). The patients who received this regimen as first-line achieved an objective response rate of 40% (6/15). One of the patients that received this therapy as second-line regimen had stable disease and the other had progressive disease. Only one patient that received as third-line had disease progression. Among six triple negative patients, only one had progressive response and this patient received chemotherapy as second-line regimen. The patient who achieved complete response had triple negative disease and received this regimen as first-line therapy. She had history of metastasectomy and had no extracranial metastases (Figure 1 and Table 6).

Overall response rates were compared within also in two patient groups to evaluate whether the time interval between the initial BC diagnosis and BM has an effect on response rates. The patients who had developed BM after a longer time interval than the median TTBM (longer than 31.6 months) and the patients who developed BM after a shorter time interval than the median TTBM (shorter than 31.6 months) had 22.2% of RR (2/9 patients) and 44.4% (4/9 patients) of RR respectively. However, this result was not statistically significant by Fisher's Exact Test (p=0.62).

Table 5. Observed Toxicities in the Study Population

Toxicity	Grade I/II		Grade III/IV	
	n	%	n	%
Leukopenia	11	61.1	1	5.6
Neutropenia	7	38.8	6	33.3
Trombocytopenia	5	27.7	1	5.6
Anemia	8	44.4	0	0
Peripheral neuropathy	6	33.3	0	0
Emesis	10	55.5	1	5.6
Hepatotoxicity	4	22.2	0	0
Nephrotoxicity	1	5.6	0	0
Ototoxicity	2	11.1	0	0

Progression-free survival (PFS)

Median PFS at median 10.8 months (range: 3.7-37.1) of follow-up time was 5.6 months (range: 2.4-8.8 months, 95%CI). Median PFS of the patients younger than 50 years was 5.6 months (range: 1.5-9.6 months, 95%CI), while median 6.6 months (range: 2.5-10.7 months, 95%CI) of PFS were achieved by patients older than 50 years old (p=0.86).The patients who had undergone metastasectomy (n=7) had median 6.6 months (range: 2.7-10.6 months) of PFS, while the patients without metastasectomy (n=11) had median 5.6 months (range:1.6-9.5months, 95%CI) of PFS (p=0.18). The PFS of the patients with extracranial metastases (n=13) were shorter than that of the patients with only cranial metastases (n=5) (range: 5.1 vs 7.2 months, 95%CI, p=0.85). Median PFS was 6.6 months of (range: 4-9.3 months, 95%CI) in patients

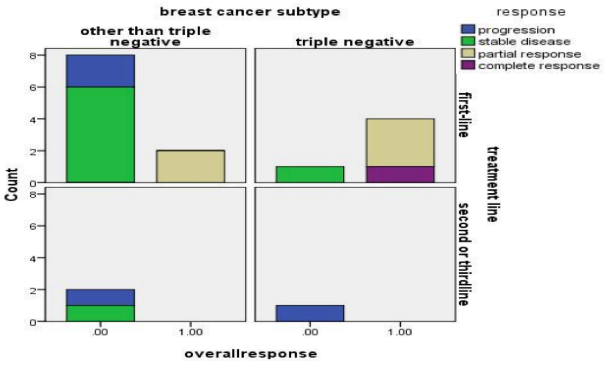

Figure 1. Overall Response Rate Comparison between the Patients with Triple Negative Breast Cancer and with Breast Cancer Patients Other Than Triple Negative Subtype

Table 6. Overall Response Rates and PFS Analysis According to Clinicopathological and Treatment Factors

Variable		Objective response rate %	p	Median PFS (months)	95%CI	P
Age	≤50	27.2		5.6	1.5-9.6	
	>50	42.8	0.62	6.6	2.5-10.7	0.86
Extracranial met						
	Yes	30.7		5.1	1.8-8.4	
	No	40	1	7.2	3.7-10.7	0.85
Metastasectomy						
	Yes	28.6		6.6	2.7-10.6	
	No	36.3	1	5.6	1.6-9.5	0.18
Line	First	40		6.6	4-9.3	
	Second or third	0	0.51	3.5	3.1-3.8	0.35
Breast cancer subtype						
	Triple negative	66.6		7.4	2.4-12.3	
	HER2positive	12.5		5	2.6-7.4	
	HR positive	25	0.09	3.6	1.02-6.9	0.3
Number of metastases						
	<2 lesions	33.3		7.2	5.5-8.8	
	>2 lesions	33.3	0.52	3.8	3.08-4.6	0.09
ECOG score						
	0-1	27.2		7.2	4.8-9.6	
	2-3	42.8	0.62	5.06	1.3-8.8	0.24

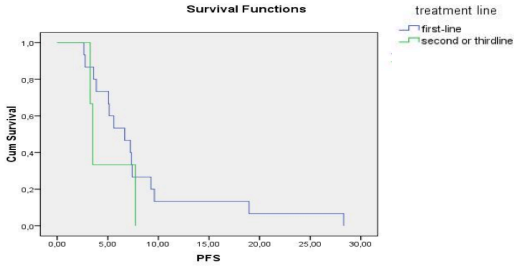

Figure 2. PFS Analysis According to the Treatment Line

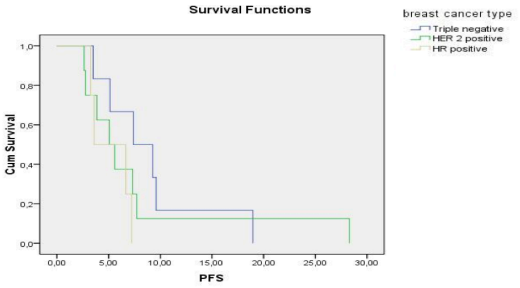

Figure 3. PFS Analysis According to the Breast Cancer Subtype

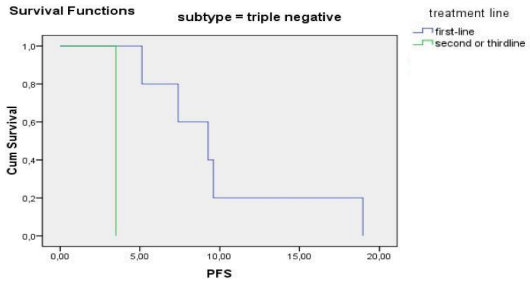

Figure 4. PFS Analysis in Patients with Triple Negative Breast Cancer According to the Treatment Line

who received this therapy as first-line regimen (n=15), it was 3.5 months (range: 3.1-3.8 months, 95%CI) in patients who were treated as second or third-line regimen (n=3) (p=0.35) (Figure 2). Median PFS according to the breast cancer subtypes demonstrated that the patients with TNBC had 7.4 months (range: 2.4-12.3 months) of PFS, HER2 positive patients had median 5 months (range: 2.6-7.4 months), and HR positive had median 3.6 months (range:2.1-6.9 months) of PFS (p=0.30) (Figure 3). Median PFS was 9.2 months (range: 5.2-13.2 months) in patients with TNBC who received this therapy as first-line regimen. However when they received as second or thirdline median PFS was shortened to 3.5 months (Figure 4) The patients with breast cancer subtype other than TNBC that received this regimen as first-line had median 5 months (range: 2.3-7.7 months) of PFS (p=0.73) (Summarized in Table 6). PFS times was compared among the patient groups designed according to TTBM. Median PFS was approximately similar between the patients with TTBM longer than median value and the patients with TTBM shorter than the median value (median 5.1 months vs. 6.6 months, 95%CI; p=0.83).

Discussion

The brain is the fourth most common metastatic site after bone, lungs and liver in breast cancer patients (Boogerd, 1996) and the development of brain metastases significantly affect the morbidity and mortality of the patients. Younger age (Tsukada et al., 1983; Carey et al., 2004), advanced stage (Carey et al., 2004; Ryberg et al., 2005), negative hormon receptor status (Samaan et al., 1981; Maki and Grossman, 2000) and HER2 overexpression (Gabos et al., 2006; Nam et al., 2008) are some of the reported risk factors for development of brain metastases. Survival after brain metastases is poor; it may be as short as 1-2 months for patients without treatment (DiStefano et al., 1979), while 8-10 months of survival times are reported for patients with systemic chemotherapy (Lee et al., 2008; Arslan et al., 2011; Kim et al., 2012). Although HER2 overexpression is a poor prognostic factor, the survival times of the HER2 positive patients with brain metastases treated with antiHER2 therapy (trastuzumab) are longer than the triple negative or HR(+) patients (Bendell et al., 2003; Kirsch et al., 2005; Nam et al., 2008). This positive effect was attributed to the systemic disease control despite ineffective blood-brain barrier cross of the trastuzumab. Triple negative patients with brain metastases have the poorest prognosis compared to other biological subtypes (Niwinska et al., 2010). Median survival after central nervous system involvement in triple negative breast cancer (TNBC) patients are reported between 3.4-6.6 months (Eichler et al., 2008; Nam et al., 2008; Arslan et al., 2011). Due to the lack of hormon receptor and HER2 expression there is not any systemic treatment option except chemotherapy for TNBC. Basal like breast cancer is a subtype which has the same phenotypic features with TNBC, however is identifed by using mRNA gene expression profiling different from TNBC. All of the basal-like tumors show triple negative characteristics, however not all but some of the triple negative cancers are basal-like. EGFR overexpression, c-kit overexpression and BRCA1 mutations are demonstrated especially in triple negative patients with basal-like genotype (Valentin et al., 2012). The treatment options blocking these targets have been evaluated by some studies recently. However there is not any available antitarget agent for triple negative patients yet.

BRCA has a function of repairing DNA double strand breaks (Ashworth, 2008). BRCA mutation can occur by genetic inheriting or sporadicly in basal-like breast cancer, or another reason for dysfunctional BRCA is lower BRCA protein expression in basal-like breast cancer. It is well known from several previous studies that BRCA1carriers are more sensitive to DNA alkylating agents such as platinum salts (Husain et al., 1998; Shen et al., 1998; Byrski et al., 2009). A recent preclinical study demonstrated that overexpression of p63 (a p53-related transcription factor) and p73 (p53 associated as well) is common among triple negative cases and associated with sensitivity to cisplatin (Leong et al., 2007). However, clinical data regarding the benefit of platinum agents in TNBC compared with other subtypes is conflicting. In a retrospective study evaluating the efficacy of platinum-based regimen in metastatic breast cancer, the ORR in TNBC patients was similar with the hormone receptor positive subgroup (Uhm et al., 2009). The efficacy of the Cisplatin-Gemcitabine regimen in a subset of heavily

treated breast cancer patients with BM was reported only by an abstract in ASCO 2010 previously (Gorbunova et al., 2010). In that study, ORR was 35.7% (2/14 patients had complete response, 3/14 patients had partial response) and median PFS was reported as 6 months which is almost similar with our results. Grade III/IV neutropenia and Grade III/IV trombocytopenia was reported as 30.5% and 19.3% respectively; severe trombocytopenia rates of our study was lower than that study; this result may be due to the lower dose of Cisplatin in our study compared with that analysis (30 mg/m^2 d1-8 vs 50 mg/m^2 d1-8). In our study we retrospectively investigated the efficacy and toxicity of Cisplatin-Gemcitabine combination in a subset of breast cancer patients at any-line after diagnosis of BM. One/third of the study population included triple negative patients. Response rate analysis according to the breast cancer subtypes showed that the patients with TNBC had an objective response rate of 66.6%, while other subtypes (HR positive and HER2 positive) had 16.6% of objective response rate. Additionally PFS analysis according to the BC subtypes demonstrated that median PFS in TNBC patients was 7.4 months while it was approximately 5.6 months in other subtypes. When the patients received this regimen as first-line regimen after BM, triple negative patients achieved median 9.2 months of PFS, however the patients with subtypes other than triple negative had median 5 months of PFS. Although our study group included low number of patients, the number of the patients in each BC subtype was almost equal and both response rates and PFS times were better in patients with TNBC than the patients with other subtypes.

Limitations of the study, as we mentioned above, the study population was restricted to a single center and therefore include only 18 patients of which 6 of them were TNBC. We did not perform gene expression profiling to define the breast cancer subtypes; we used only phenotypical, immunohistochemical characteristics to define the BC subtypes. Therefore, we do not know whether the TN patients in this study are also basal-like or not.

In conclusion, Cisplatin-Gemcitabine combination regimen is an effective and well-tolerated regimen for breast cancer patients with BM. Due to the heavily-treated nature of these patients, G-CSF prophylaxis should be used in each cycle. Although the study group includes only 18 patients, higher response rates and longer PFS times in patients with TNBC suggests that this regimen may be an option as first-line chemotherapy regimen for TNBC patients compared to other subtypes. However, prospective and multicenter studies including the breast cancer patients with brain metastases and analysing the BC subtypes according to gene expression profiling are required to support this hypothesis.

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