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Original Article

Survival analysis of single agent gemcitabine therapy in patients with metastatic breast cancer

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Abstract

Aim: Gemcitabine has demonstrated experimental and clinical antitumor activity in various human neoplasms including pancreas, ovary, non-small cell lung and breast tumors. We aimed to investigate the factors affecting progression-free survival (PFS) and overall survival (OS) of patients who received single agent gemcitabine for metastatic breast cancer.

Material Methods: Twenty-eight patients with metastatic breast cancer who were treated with gemcitabine in Gaziantep University Medical Faculty Medical Oncology Department between March 2007 and December 2018 were evaluated retrospectively. Gemcitabine 1000 mg / m2 was administered as a single agent treatment on the 1st and 8th days, every 21 days.

Results: Twenty-seven (96.4%) of the patients were female and 1 (3.6%) was male. The median age was 52 years(range 35-76). Median PFS was 5 months (95% confidence interval 2,41-7,58) and median OS was 26 months (95% confidence interval 11,73-40,26). The median PFS of the patients with only lung metastasis was 16 months and the other patients were 4 months (Log-rank p = 0.020)

Conclusion: Gemcitabine is a very well tolerated agent with sufficient efficacy for patients with metastatic breast cancer who were preferred to use single agent chemotherapy than combination therapies. Patients with only lung metastasis may benefit more from single agent gemcitabine in metastatic breast cancer.

Keywords: Metastatic breast cancer; gemcitabine; progression-free survival; overall survival.

INTRODUCTION

Breast cancer is the most common malignancy in women worldwide (1). At the time of diagnosis, approximately 10% of patients are locally advanced or metastatic. Approximately 30% of patients treated in early stage disease develop metastasis during follow-up. Despite advances in cancer treatment, mortality in metastatic breast cancer (MBC) remains high (2).

Anthracyclines and taxanes are frequently involved in the treatment of adjuvant and neoadjuvant breast cancer (3). Patients with recurrence or metastasis have mostly used these treatment alternatives before. In case of re-use of these agents, ongoing toxicities or treatment resistance such as dose-dependent cardiotoxicity or neuropathy are observed in patients (4). Therefore, all factors should be reviewed when planning treatment.

Gemcitabine (2′, 2′-difluorodeoxycytidine) is a pyrimidine analogue that inhibits DNA synthesis. It has demonstrated experimental and clinical antitumor activity in various human neoplasms including pancreas, ovary, non-small cell lung and breast tumors (5).

Since gemcitabine can provide similar survival data with other agents with its low toxicity profile and ease of use, we think that it is one of the most suitable agents for metastatic breast cancer. In this study, we aimed to investigate the factors affecting progression-free survival (PFS) and overall survival (OS) of patients who received single agent gemcitabine for metastatic breast cancer.

MATERIAL and METHODS

Twenty-eight patients with metastatic breast cancer who were treated with gemcitabine in Gaziantep University Medical Faculty Medical Oncology Department between

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March 2007 and December 2018 were evaluated retrospectively. This study was approved by the Institutional Ethics Committee and conducted in compliance with the ethical principles according to the Declaration of Helsinki.

Inclusion criteria; 18 years of age and older, histologically proven breast cancer diagnosis, administration of gemcitabine chemotherapy regimen, measurable metastatic disease according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria, and adequate liver, kidney and bone marrow function. Those who did not meet the inclusion criteria were excluded. Patients' demographic information (age, sex, concomitant disease), histopathological and molecular subtypes, history of breast surgery, presence of metastasis at the time of diagnosis, metastasis sites, treatment prior to gemcitabine treatment, the starting and ending date of gemcitabine, the number of cycles, the reason for cessation of gemcitabine, side effects, last follow-up and exitus dates were recorded.

Gemcitabine 1000 mg / m2 was administered as a single agent treatment on the 1st and 8th days, every 21 days.

Tumor response was assessed by computerized tomography (CT) or positron emission tomography / computed tomography (PET / CT) every 9-10 weeks according to RECIST v1.1 criteria. Hematological and other toxicities were evaluated.

Statistical Analysis

All results were presented as the rate for categorical values or mean/median for continuous variables. To detect significant differences between qualitative variables, Chi-square and/or Fischer-exact test for rates, and t-test for continuous variables were used. Quantitative variables were described as means with standard deviation [SD]), while qualitative variables were presented as frequencies with proportions. RFS and OS estimated by Kaplan-Meier method and long-rank test was used for the univariate analysis.

RESULTS

Twenty-seven (96.4%) of the patients were female and 1 (3.6%) was male. The median age was 52 (35-76 years). Histopathologically; 25 (89.3%) patients had invasive ductal carcinoma, 3 (10.7%) patients had invasive lobular carcinoma. When the molecular subtypes are evaluated; 10 (35.7%) patients were luminal A, 6 (21.4%) patients were luminal B (her2-), 2 (7.1%) patients were luminal B (her2 +), 3 (10.7%) patients were Her2 +, 7 (25%) patients were triple negative / basal-like. Eight-teen(64.3%) of the patients were hormone receptor positive and 5(17%) patients were Her2 status positive. Patients characteristics were summerized in Table 1.

Six(21.4%) patients had only bone metastasis, 3 (10.7%) patients had liver metastasis, 3 (10.7%) patients had only lung metastasis, and the remaining patients had metastasis in multiple organs.

Table 1. Patient Demographics and Baseline Features

Characteristic,	N (%)
Demographics	
Age (Years):	
25-45	7(25)
46-65	18(64.3)
Above 65	3(10.7)
Mean	53.75
Gender	
Female	27(96.4)
Male	1(3.6)
Histological type	
Invasive ductal carcinoma	25(89.3)
Invasive lobular carcinoma	3(10.7)
Molecular Subtype	
Luminal A	10(35.7)
Luminal B Her2 -	6(21.4)
Luminal B Her2 +	2(7.1)
HER2 +	10(35.7)
Triple Negative/Basal Like	7(25)

Median 4.5 (2-28) cycles of gemcitabine were administered to the patients. All patients received at least 2 lines of treatment prior to gemcitabine. Grade 3 neutropenia developed in 1 (3.6%) patient and grade 4 thrombocytopenia developed in 1 (3.6%) patient. Dose skipping was required in 2 (7.1%) patients and dose reduction was performed in 2 (7.1%) patients. Only one patient (3.6%) was discontinue treatment due to toxicity.

Survival Analysis

In survival analysis, median PFS was 5 months (95% confidence interval 2,41-7,58) and median OS was 26 months (95% confidence interval 11,73-40,26).(Figure 1)

When the factors affecting PFS and OS were evaluated, the median PFS of the patients with only lung metastasis was 16 months and the other patients were 4 months (Log-rank p = 0.020)(Figure 2). The difference was statistically significant. No other statistically significant association between the parameters and survival outcomes were found. Hormone receptor and Her2 status did not have affect on survival parameters.

DISCUSSION

Although metastatic breast cancer is commonly incurable, patients' average life expectancy is prolonged due to improvements in systemic chemotherapy, endocrine therapy, and immunotherapy. Systemic chemotherapy is the basis of treatment in patients with visceral organ involvement and dysfunction. Single agent gemcitabine treatment has been shown to have less side effects than other cytotoxic therapies in patients with metastatic breast cancer who have a high quality of life. (6). Response rates are higher in combination therapies, but toxicity increases and does not provide significant survival benefit (7). Response rates of single agent gemcitabine

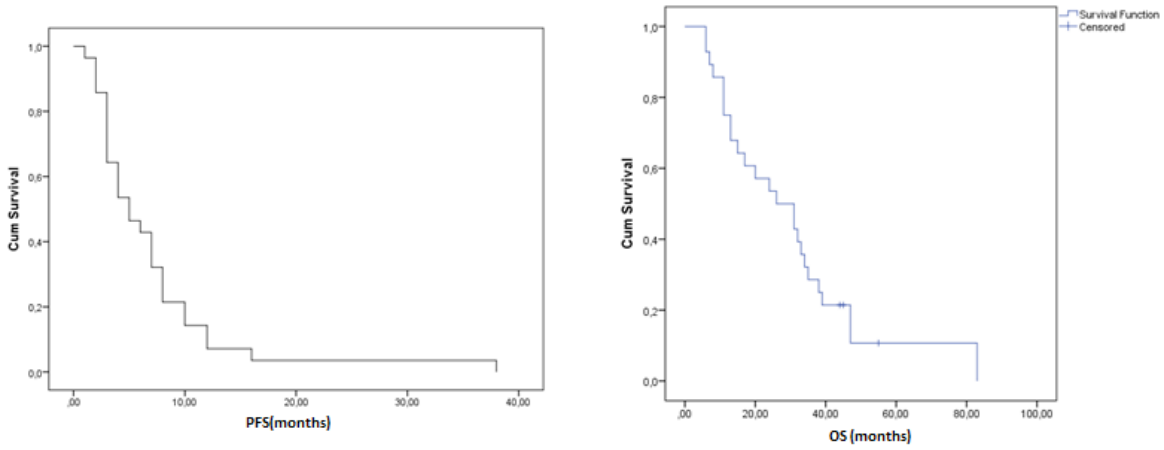

Figure 1. Kaplan-Meier curves for progression-free survival(PFS) and overall survival(OS)

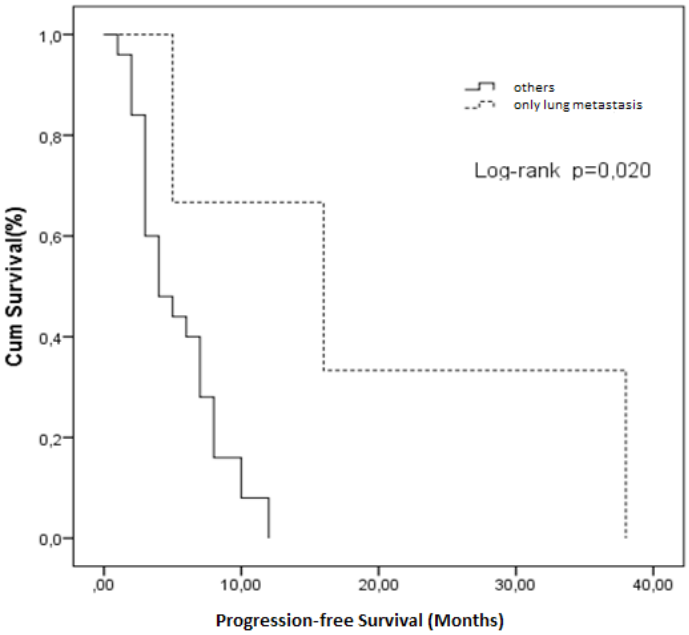

Figure 2. Comparison of PFS of patients with only lung metastasis and others by Kaplan-Meier curve.

chemotherapy were reported as 36% in the first line chemotherapy, 28% in the second line chemotherapy, and 16% in a study evaluating the second and third line combination (8,9). In our study, the number of treatment lines received by patients was heterogeneous but at least 2 and above. Median 4.5 (2-28) cycles of gemcitabine were administered to the patients in our study and our response rates were similar to the literature.

In the literature, there are studies showing progression-free survival of 3-7 months and overall survival of 10-25 months with gemcitabine monotherapy in metastatic breast cancer (10,11).Sezgin et al. evaluated the treatment of gemcitabine in patients who had previously received anthracycline and taxane treatment. Progression-free survival was 5 months and overall survival was 20 months in this study (12). In our study, a similar progression-free survival and a higher overall survival (26 months) were detected. Also we found that single agent gemcitabine treatment had more PFS benefit in patients with only lung metastases who had previously received intensive treatment in advanced breast cancer patients.

In our study, the distribution of molecular subtypes was found to be consistent with other studies. Survival analysis did not reveal any subtypes among the subtypes that showed advantages or disadvantages. Similar results have been obtained in other studies using gemcitabine in metastatic breast cancer (10,11).

Gemcitabine doses have been administered differently in previous studies, and mild to moderate hematological toxicities and tolerable side effects have been reported(8,13). In our study, the side effect rates were low and grade 3-4 side effects were observed only in 2 patients.

Limitations of this study were retrospective analysis and limited number of patients. The difference in progression-free survival, especially in patients with lung metastasis, is remarkable. However, more robust prospective clinical trials are needed to make this claim stronger.

CONCLUSION

Gemcitabine is a very well tolerated agent with sufficient efficacy for patients with metastatic breast cancer who were preferred to use single agent chemotherapy than combination therapies. Patients with only lung metastasis may benefit more from single agent gemcitabine in metastatic breast cancer.

Competing interests: The authors declare that they have no competing interest.

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