

Original article

Prognostic Factors for Treatment Outcomes of First Line Chemotherapy in Metastatic Breast Cancer

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Background: A large number of old and new chemotherapeutic agents are now used in the treatment of metastatic breast cancer (MBC) patients. The choice of chemotherapy regimen depends on several factors concerning not only the tumor's characteristics, but also the patient preference, so the clinician must identify the prognostic factors that may help in tailoring treatment to each patient. The aim of the study was to evaluate the prognostic factors for response, time to tumor progression (TTP) and overall survival (OS) after the first line chemotherapy for MBC.

Patients and Methods: The study included 30 eligible women who had measurable metastatic disease and prior anthracycline based treatment in the adjuvant setting. All patients received cisplatin 75 mg/m² on day 1 and gemcitabine 1000 mg/m² on days 1&8 of 21-day-cycles to a maximum 8 cycles. Prognostic factors studied were performance status (P.S), age, grade, menopausal status, hormonal receptor status, disease free interval (DFI) and number of metastatic sites.

RESULTS: Partial response was found in 43.3% (13) of the patients. Median TTP was 10 months. Median OS was 12 months. Prognostic factors significant for response were performance status (P=0.04), number of metastatic sites (P=0.02) and disease free interval (P=0.002). Prognostic factor for TTP was performance status (P=0.03), for overall survival performance status (0.009) and hormonal receptor (P=0.008).

Conclusion: Prior to the initiation of first line chemotherapy for metastatic breast cancer, it is necessary to evaluate the performance status, number of metastatic sites and disease free interval to tailor treatment to achieve maximum benefit for the patients.

Key words: Metastatic breast cancer, gemcitabine plus cisplatin, prognostic factors.

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INTRODUCTION

Breast cancer, the most frequent malignancy in women, is a global problem and a leading cause of cancer mortality¹. Median survival from diagnosis of metastatic disease is 2 to 3 years, with 5% to 10% survival beyond 5 years².

The treatment goal in women with advanced breast cancer include prolongation of life, control of tumor burden, reduction in cancer-related symptoms or complications and maintenance of quality of life and function³.

Cytotoxic chemotherapy remains a mainstay of treatment for women with breast cancer, irrespective of hormonal-receptor status and is the backbone of many novel treatments incorporating biological therapy. Chemotherapy has substantial side effects including fatigue, nausea, vomiting, myelosuppression, neuropathy, diarrhea and alopecia. For this reason, treatment of women with chemotherapy for advanced disease involves tradeoffs between palliation and toxicity of therapy⁴.

The widespread inclusion of anthracyclins in the adjuvant setting and concerns regarding cardiotoxicity limit their use as first-line therapy in metastatic disease. During the past decade, other cytotoxic drugs with activity in advanced breast cancer were identified, including taxanes, gemcitabine, vinorelbine and capecitabine⁵.

Among several agents that have been used in metastatic breast cancer, gemcitabine and platinum compounds have been well-characterized single agents^{6,7}. Synergism between gemcitabine (a compound that inhibits DNA repair) and cisplatin (a compound that induces DNA damage) has been demonstrated in vitro studies. Exposure to gemcitabine can counteract the cisplatin resistance that results from the up-regulation of DNA repair processes. Cisplatin enhances the rate of incorporation of gemcitabine leading to apoptosis⁸.

Clinically, these agents have partially non-overlapping toxicity, as gemcitabine does not enhance cisplatin-

induced nephrotoxicity or neurotoxicity and cisplatin causes only mild myelosuppression⁹.

Well established clinical factors can predict the likelihood of response to therapy and long-term treatment outcomes in women with metastatic breast cancer. Patients who have received less therapy, have a longer disease-free interval since initial diagnosis, soft tissue or bone metastasis, fewer symptoms and better performance status are more likely to experience longer survival with metastatic disease than heavily treated patients with shorter treatment intervals, visceral metastasis and greater symptomatology³.

The most relevant prognostic factors for predicting survival from the time of metastatic occurrence are age at initial diagnosis, hormonal receptor status and site of metastasis. It is also shown that the metastases interval is an easily assessed and valuable multifactorial prognostic index reflecting the multiparametric variability of the disease¹⁰.

A prognostic factor is defined as a measurement taken at the time of diagnosis or surgery that is associated with outcome (e.g. overall survival, disease-free survival or local control). They are used to estimate outcome following specific systemic therapy. Mathematically a prognostic factor is demonstrated as a statistically (and clinically) significant separation of curves outcome that are based on the presence or absence of the factors in a Cox proportional hazard ratio³.

The aim of the study was to identify the significant prognostic factors for treatment outcome of first line chemotherapy (gemcitabine and cisplatin) in metastatic breast cancer. The prognostic factors may assist physicians in evaluation of patients and in directing them toward the appropriate therapeutic decision.

PATIENTS AND METHODS

The study included all patients with metastatic breast cancer who presented to the Clinical Oncology department, Assiut University Hospital between March 2006 to September 2008 (30 eligible cases). All the patients were evaluable for response, toxicity and prognostic factors. The median follow-up time was 12 months (range 6-24 months).

Eligibility Criteria:

Eligible women had metastatic breast carcinoma with the following criteria: minimum of one bidimensionally measurable lesion by radiographs, Eastern Cooperative Oncology Group performance status (0-2), adequate bone marrow reserve and liver and renal functions. The cancer

must be metastatic after adjuvant anthracycline-based regimen. Prior gemcitabine or cisplatin was not allowed, nor was any prior chemotherapy for metastatic disease.

Study Design:

All patients received cisplatin 75mg/ m2 intravenous infusion over 1 hour on day 1 with pre-hydration measures and antiemetics plus gemcitabine 1000 mg/ m2 intravenous infusion over 30 minutes on day 1 and 8. Chemotherapy was given every 21 days for a maximum of 8 cycles or until disease progression, intolerable toxicity, or patient withdrawal.

Study Evaluation:

Before the study, patients underwent complete medical history, physical examination and evaluation of performance status.

Radiological evaluation included chest x-ray or computed tomography (CT), abdominal ultrasound or CT to identify visceral disease and bone scan. CT or magnetic resonance of the central nervous system was symptom driven. Radiographic evaluation was performed before initial protocol treatment and repeated after the initial 3 cycles and then after every two subsequent treatment cycles.

Complete blood counts before treatment and every treatment cycle were done.

Response was assessed according to WHO criteria. A complete response (CR), partial response (PR) or stable disease (SD) was confirmed 4 weeks after first observation of the response. Time to tumor progression was calculated from the initiation of treatment to the first observation of disease progression. Overall survival was calculated from the start of treatment to the date of death or last visit date.

Toxicity was evaluated by National Cancer Institute Toxicity Criteria version 2 after each cycle.

Statistical Methods:

This trial was designed to identify the significant prognostic factors for response, time to tumor progression (TTP) and overall survival (OS).

Time to tumor progression and overall survival were assessed using Kaplan-Meier method.¹¹

Prognostic factors for OS, TTP and response rate (RR) were analyzed by use of Cox regression analyses.

RESULTS

Thirty women entered this study and all of them were assessable for efficacy and toxicity. All patients had been

previously treated with anthracycline-based regimen as adjuvant treatment.

The median age of the patients was 49 years (range: 30-60 years). The median follow-up duration was 12 months (range: 6-24 months)

Table (1) shows patient characteristics.

The outcomes of patients treated with cisplatin and gemcitabine was as follow: PR was achieved in 13 patients out of 30(43.3%), ten patients (33.3%) had SD and 7 patients (23.3%) had PD.

The most common grade 3/4 toxicities included thrombocytopenia in 6 patients(20%), nausea and vomiting in 6 patients (20%), neutropenia in 4 patients(13%), anemia in one patient(3%) and febrile neutropenia in one patient(3%). There was no treatment related deaths.

For metastasis, the lung was the most common metastatic site (14 patients, 46.6%), bone (13 patients, 43%), skin and soft tissue (12 patients, 40%), liver (7 patients, 23%), lymph nodes (3 patients, 10%) and brain (2 patients, 8%).

Table (2) shows the univariate analysis of prognostic factors for response. Performance status ($p=0.04$), number of metastatic site ($p=0.02$) and disease free interval ($p=0.002$) were significant prognostic factors for response.

Table (3) shows prognostic factors for time to progression. Performance status was the only prognostic factor for TTP ($p=0.03$).

Table (4) shows the prognostic factors for overall survival. Performance status (P.S) ($p=0.009$) and hormonal receptor positive ($P=0.008$) were significant prognostic factors for OS.

Figure (1) shows the median time to progression (10 months, 95% CI 8.2-11.8) and one year time to tumor progression was 14%.

Figure (2) shows the median overall survival (12 months, 95% CI 11.2-12.8). One and two years overall survivals were 43.5% and 10.9%, respectively. One and two years disease free survivals were 48.5% and 5%, respectively.

Table 1: Patient characteristics.

Characters	Frequency	%
Performance Status (Eastern Cooperative Oncology Group)		
0	15	50.0
1	8	26.7
2	7	23.3
Menopausal status		
Pre	16	53.3
POST	14	46.7
Hormonal status		
Negative	17	56.7
Positive	13	43.3
Tumor grade		
2	14	46.7
3	16	53.3
Disease free interval		
<1 year	18	60.0
>1 year	12	40.0
Number of metastases		
1	11	36.7
2	16	53.3
3	2	6.7
4	1	3.3

Table 2: Univariate analysis for prognostic factors for response to gemcitabine plus cisplatin as first line regimen for metastatic breast cancer.

		Response			p-value
		PD	PR	SD	
Performance Status	0+1	4 44.2%	12 92.3%	7 70.0%	0.04*
	2	3 42.9%	1 7.7%	3 30.0%	
grade	2	3 21.4%	6 42.9%	5 35.7%	0.95*
	3	4 25%	7 43.8%	5 31.2%	
No of metastasis site	1	1 9.1%	5 45.5%	5 45.5%	0.02*
	2	3 18.8%	8 50%	5 31.2%	
	3	3 100%	0 0	0 0	
Menopausal status	Pre	5 31.2%	5 31.2%	6 37.55	0.3*
	post	2 14.35	8 57.1%	4 28.4%	
Age		44.29±7.3	48±10.4	46.4± 10.2	0.4**
Disease free interval		10 ± 1.5	24± 1.2	12± 1.5	0.002***

*fisher exact test, ** Kruskal-Wallis test, *** log rank test

Table 3: Prognostic factors for time to progression (Kaplan Meir analysis) of 30 metastatic breast cancer patients treated by gemcitabine plus cisplatin as first line regimen.

		Median	Std. Error	95% Confidence Interval		P-value Log Rank (Mantel-Cox)
				Lower Bound	Upper Bound	
grade	2	10	0.73	8.57	11.43	0.58
	3	10	1.83	6.40	13.59	
Hormonal receptor	negative	8	0.91	6.20	9.79	0.07
	positive	10	1.04	7.95	12.04	
Performance status	1	10	0.51	8.99	11.08	0.03
	2	8	0.61	6.79	9.21	
Number of metastatic sites	1	11	2.02	7.02	14.97	0.3
	2	10	0.67	8.68	11.31	

Table 4: Prognostic factors for overall survival (Kaplan Meir analysis) of 30 metastatic breast cancer patients treated by gemcitabine plus cisplatin as first line regimen.

		Median	Std. Error	95% Confidence Interval		P-value Log Rank (Mantel-Cox)
				Lower Bound	Upper Bound	
grade	2	12	2.38	7.32	16.67	0.8
	3	12	0.93	10.17	13.82	
Hormonal receptor	negative	12	0.60	10.80	13.19	0.008
	positive	18	1.75	14.56	21.43	
Performance status	1	13	1.29	10.45	15.54	0.009
	2	10	1.19	7.65	12.34	
Number of metastatic sites	1	12	0.82	10.38	13.61	0.3
	2	12	1.32	9.41	14.58	

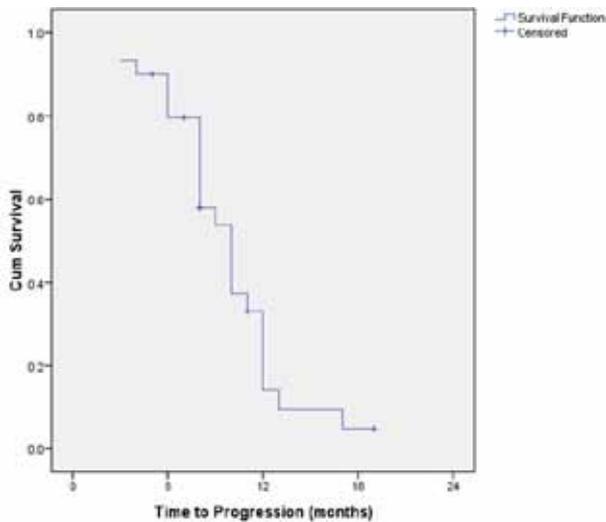


Figure 1: Time to progression (TTP) of 30 metastatic breast cancer patients treated by gemcitabine plus cisplatin as first line regimen, Median TTP 10 months 95% CI (8.2-11.8), One year TTP=14.2%

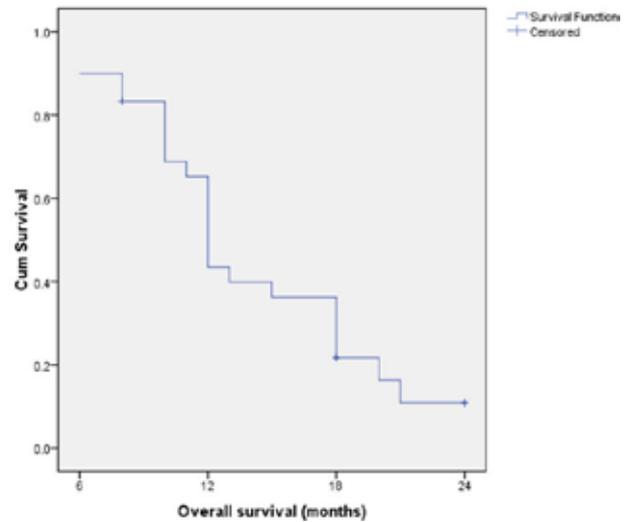


Figure 2: Overall survival (OS) of 30 metastatic breast cancer patients treated by gemcitabine plus cisplatin as first line regimen, Median OS 12 months 95% CI (11.2-12.8), One year survival rate= 43.5%, 2 year survival rate= 10.9%.

DISCUSSION

Metastatic breast cancer (MBC) is a highly heterogenous disease where particular criteria must be considered, taking into account not only the clinical and biological parameters but also patient expectation and preference. The objectives of an optimal chemotherapy CT for MBC are to prolong survival and enhance the quality of life with minimal toxicity. The therapeutic strategy may include sequential single agents or combination CT.^{12,13}

In daily practice, the choice of CT regimen depends on several factors concerning not only the tumor's characteristics but also the patient, so the clinician must consider the following: if the patient underwent prior CT (including previous adjuvant treatment); if she has a good performance status, or any co-morbidities, as well as the toxicity profiles: the organization of schedule and the disease's characteristics as relapse-free interval from adjuvant therapy, clinical aggressiveness, sites of metastasis. Finally, but no less important, the clinician also must consider the patient's preference¹⁴.

Cisplatin-gemcitabine is a synergistic chemotherapy combination highly proven in a broad spectrum of epithelial neoplasms and shows a non-cross-resistance profile with the most active drugs in metastatic breast cancer¹⁵. The US Food and Drug Administration approved an indication for gemcitabine therapy for women with advanced breast cancer based on the highly significant prolongation of time to progression (TTP)¹⁶ and interim promising overall survival (OS)¹⁷.

The toxicity profile is an important factor in determining optimal combination therapy: balancing of efficacy and safety is a key goal for delivering a positive risk-benefit profile for each patient. Gemcitabine, capecitabine and docetaxel are highly active agents in anthracycline-pretreated metastatic breast cancer. A phase III trial compared gemcitabine plus docetaxel versus capecitabine plus docetaxel providing valuable information for a clinician in choosing an optimal treatment. This study showed that gemcitabine plus docetaxel is an active regimen in advanced breast cancer with similar efficacy to capecitabine plus docetaxel, but the toxicity profile favours gemcitabine plus docetaxel¹⁸.

Most patients with a diagnosis of advanced breast cancer present having received previous adjuvant treatment. The adjuvant chemotherapy is particularly important for the choice of the optimal first chemotherapeutic approach to advanced disease¹⁴. The relationship between the activity of first line chemotherapy for MBC and prior adjuvant treatment is controversial, since some studies showed a poorer outcome¹⁹ whereas others demonstrated an outcome similar to patients who had not received previous adjuvant therapy²⁰.

The site(s) and degree of metastatic dissemination are among the principle prognostic factors for patients with MBC. Patients with visceral metastasis to the liver and/or lung have a very poor prognosis. Although good performance status (P.S), restricted disease dissemination and limited extent of metastasis infiltration are associated with higher response to chemotherapy, responses are generally short lived, with rapid disease progression

after treatment failure. Thus novel strategies for the management of patients with MBC with visceral metastasis are urgently needed²¹.

In this study, a response rate (RR) of 43.3%, a median survival of 12 months and a median TTP of 10 months were achieved. Variable treatment outcomes of gemcitabine-cisplatin (GP) combination have been reported by others. A response rate of 54.5%, a median OS of 14.8 months and a TTP of 8 months has been reported by Mohran²². Burch et al.²³ reported RR of 29%, OS 13 months and a TTP 7 months. Kim et al.²⁴ reported RR 28.9%, median OS 19.5 months and a TTP 5.2 months. Wang et al.²⁵ reported a RR of 62.2%, a TTP 6.2 months. The difference in RR and OS observed among these studies, including this study, most likely reflect patient selection with good prognostic factors as longer disease free interval (DFI), higher percentage of patients who had one metastatic site, hormonal receptor positive and HER-2 negative. The lower RR in the study of Burch²³ and Kim et al.²⁴ are due to the use of GP combination as a second line treatment for metastatic disease.

The incidence of hematological toxicity in this trial was lower than that reported in other combination chemotherapy regimens such as gemcitabine plus taxol5 and capecitabine plus docetaxel²⁶ combination which led to a 7% occurrence of grade 3 hand-foot syndrome. So the modest toxicity profile of GP combination regimen favors its use in the first line treatment of MBC.

For the prognostic factors, P.S, number of metastatic site and disease free interval (DFI) were prognostic factors for response. This is in agreement with Kramer et al.²⁷ who reported that DFI ($p=.009$) and multiple sites of visceral metastasis ($p=.037$) were significant prognostic factors for response in multivariate analysis.

In this study, P.S was the only significant prognostic factor for TTP; Kim et al.²⁴ reported the same result.

Koshy et al.²⁸ reported a reduced risk of progression for triple negative (lack expression of estrogen, progesterone and HER-2 neu receptors) compared to non-triple negative MBC.

In this study, prognostic factor for survival were P.S and hormonal receptor status. This is in agreement with the results of Wheler et al.²⁹, but Largiller et al.¹⁰ and Kramer et al.²⁸ added other prognostic factors for OS as age at initial diagnosis, hormonal receptor status, multiple sites of visceral disease and disease free interval.

Liu et al.³⁰ reported that Karnofsky P.S, grade, estrogen receptor status, stage, number of lymph nodes,

liver metastasis, DFI, number of metastasis had a significant impact on survival.

Bai et al.³¹ reported that $P.S>1$, multiple brain metastasis without whole brain irradiation in combination with chemotherapy were associated with poor prognosis.

Chew et al.³² analyzed polymorphism in genes in relation to gemcitabine-cisplatin combination treatment in metastatic breast cancer. They concluded that polymorphism was significantly associated with clinical outcomes and may tailor which patients benefit from this regimen.

CONCLUSION

Prior to the initiation of first line chemotherapy for patients with metastatic breast cancer and previous anthracycline based adjuvant therapy, it is necessary to evaluate the performance status, disease free interval and number of metastatic sites as prognostic factors for treatment outcomes. This study implicates the importance of searching for new prognostic and predictive factors and underscores the importance of the validated markers and patients characteristics in metastatic breast cancer that may assist the clinician to tailor treatment to achieve maximum benefit for the patients.

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