Gemcitabine/Cisplatin in the treatment of metastatic breast cancer patients pretreated with anthracyclines

Atef Riad, MD[1], Eman El-Sheikh, MD[1], Niviene Gado, MD[1], Hatem Abdallah, MD[1], Amr Shafik, MD[1]

(1) Radiation Oncology & Nuclear Medicine Dept., Ain Shams University

Corresponding Author: Dr Eman El-Sheikh, MD
Ass. Prof. of Radiation Oncology
Ain Shams University
E-mail: aser.1998@yahoo.com

Key words: Metastatic Breast Cancer, Gemcitabine, Cisplatin.

Submitted: March 2010 - Accepted: 30 May 2010

ISSN: 2070-254X

Abstract

Purpose: A phase II prospective study to evaluate efficacy and tolerability of gemcitabine and cisplatin as a first line combination chemotherapy in patients with metastatic breast cancer (MBC) pretreated with anthracyclines in their adjuvant setting.
Patients & Methods: Patients were assigned to receive gemcitabine 1250mg/m2 on days 1 & 8 plus cisplatin 75 mg/m2 day 1 , repeated every 3 weeks (for 6-8 cycles).
Results: The study included 40 female patients with MBC and took place during the period from December 2006 to June 2009 with a median follow up period of 12 months (range 3-24 ms).The overall objective response rate was 57.9%.The median duration of response was 9.5 ms (95% CI,8.07 to 11.83 ms)and the median time to disease progression was 12.5 ms (95% CI,10.85 to 14.43 ms).The estimated median survival was 22 ms (95% CI,16.34 to 27.66 ms).The 1 and 2 years survival probabilities were 68.52%and 31%, respectively .The study regimen proved to be quite tolerable with the main hematological toxicities of this protocol were grade III anemia in 10% of patients, grade III/IV neutropenia in 20% of patients and grade III/IV thrombocytopenia in 17.5% of patients. There were no grade IV non hematological toxicity observed within the study and the only grade III non hematological toxicities recorded in the study were grade III nausea in 25% of patients, grade III vomiting in 17.5% of patients, grade III fatigue in 15% of patients and grade III renal toxicity in 2.5% of patients.
Conclusion: Gemcitabine / cisplatin combination was both effective and tolerable as first-line therapy in MBC pretreated with anthracyclines. However, initiation of larger phase III studies comparing gemcitabine cisplatin combination directly with other chemotherapy combinations in MBC patients pretreated with anthracyclines is recommended.

Introduction

Metastatic breast cancer (MBC) represents 10% of newly diagnosed breast cancer patients. Moreover, a substantial portion of the early and localized breast cancer patients will metastasize sooner or later along the course of their disease.1

In spite of major advances in screening, surgery, radiation, endocrine therapy and chemotherapy of patients with early stage breast cancer, modest progress has been achieved in improving survival for women with metastases. The median survival for patients with metastases remains between 18 and 24 months.2

The primary objective of different lines of treatment for MBC patients is palliation, not cure. Treatment aims at controlling the progression of the patient's disease, improve quality of life (QOL) and improve or eliminate tumor-related symptoms.3

Endocrine therapy of MBC patients achieves objective response in more than 30% of patients that generally lasts an average of 1 year which is usually several months longer than response to chemotherapy when used in the same setting.4

However, with the overall response rate (RR) to chemotherapy being higher than that to endocrine therapy, patients with rapidly progressive tumors or major tumor-related symptoms should be considered for chemotherapy.5

Anthracycline-based regimens if not previously used in the adjuvant (adj.) setting are the first chemotherapy option in treatment of MBC, it can usually achieve an overall RR around 65% and time to progression (TTP) averaging around 12 months.6

Taxanes were used either as single agent or in combination in MBC . Single agent taxanes were found to be active in both doxorubicin-naive and doxorubicin-refractory MBC (RRs averaging between 25% to 55%) with a better toxicity profile in comparison to taxane combinations regimens but it failed to achieve survival impact.7

Taxanes were used in combination with a wide spectrum of chemotherapeutics with better RRs but on the expense of increase of the side effects percentages that could compromise the patients' QOL. In addition these RRs did not translate into a significant survival advantage added to the fact that MBC remains an incurable disease.8

Financial, reducing toxicities and QOL issues led to the usage of non-taxane active drugs like vinorelbine, capecitabine and
gemcitabine as available options for MBC treatment.8

Gemcitabine "a pyrimidine antimetabolite" was found to be both effective and safe in combination with different drugs in both locally advanced and MBC.9

Cisplatin, one of the classical chemotherapeutics had been used repeatedly as

an important agent in many active chemotherapeutic doublets in most cancer subtypes including MBC with a considerable effectiveness and good tolerance.10 Drug resistance to cisplatin may be overcome when used in combination with gemcitabine.11

The benefit gained from this combination would be maximized by using it as a first line therapy instead of second line or salvage therapy in poly treated patients where more side effects and less probability of RRs would be expected.12

In 2006, the results of Fuentes and colleagues who enrolled 46 patients with MBC to receive gemcitabine and cisplatin as first line therapy showed that 17% of patients achieved complete response "CR" and 64% achieved partial response "PR" with an overall RR of 81%. From this they concluded that gemcitabine plus cisplatin is a highly effective and safe first line treatment for patients with MBC and the TTP of 14.9 ms compares favorably with other standard treatments as anthracyclines and taxanes.13

Thus the current phase II prospective study was conducted to evaluate the efficacy & saftey of gemcitabine and cisplatin combination chemotherapy as first line chemotherapy in MBC patients previously treated with adj. anthracyclines in terms of degree of response, time to disease progression and treatment related toxicities.

Patients and methods

Eligibility criteria

Patients entered onto this study were required to have histological or cytological proven MBC with at least one bi-dimensionally measurable lesion, age ≥18 years and ≤ 65 years, performance status of 0-2 on the ECOG performance status scale 4, estimated life expectancy of at least 3 months, Adequate bone marrow reserve (neutrophils ≥ 1.5 x 10^3/ml,platelets ≥ 100 x 10^3/ ml, hemoglobin > 9 gm/dl), hepatic profile (total bilirubin ≤ 1.5 unl {upper normal level},AST and ALT ≤ 2.5 unl,alkaline phosphatase < 5 unl except in presence of bone metastasis and in absence of any liver disorders, and renal functions (Creatinine ≤ 1unl),and the calculated creatinine clearance should be ≥ 60ml/min.)

All patients must had previous treatment with anthracycline containing regimen either as adj. or neoadjuvant therapy and had no previous chemotherapy for MBC. Previous radiotherapy and hormonal therapy were permitted but hormonal therapy must be discontinued prior to enrollment.

Exclusion Criteria

Patients were excluded from the study if they had serious concomitant medical or psychiatric illness and prior or concurrent malignancy other than breast cancer. Patients with solitary brain and/or bone metastases and pregnant or lactating patients were considered ineligible for this study.

Pretreatment work up

Detailed history and clinical examination including:
Vital signs, systemic & locoregional examination, and performance status assessment. Body surface area for each patient will be calculated before initiation of treatment and every 2 cycles.

Laboratory studies

All patients performed the following Lab work prior to treatment initiation as well as prior to each chemotherapy cycle: Complete blood picture, liver function tests (AST, ALT, T. bilirubin, alkaline phosphatase), renal function tests (S. creatinine and BUN, and creatinine clearance).

Radiological studies

All patients underwent full metastatic radiological work up for disease assessment and as a base line for response evaluation after therapy: chest x-ray (CT scan of the chest was done if x-ray revealed metastatic or suspicious lesions), CT scan of the abdomen and pelvis, Isotopic bone scan, and mammography and breast ultrasound. Other radiological investigations were done when clinically indicated.

Treatment strategy

All eligible patients fulfilling the inclusion criteria and after the pretreatment assessment received Gemcitabine 1250mg/m^2 administered as a 30-minute intravenous infusion on days 1 and 8 plus cisplatin 75mg/m^2 on day 1. The treatment cycle was repeated every 3 weeks. Cisplatin was administered intravenously during a 2-hour period of forced hydration with standard pre and post-treatment hydration. Infusion of 250 ml of 5% dextrose or normal saline containing 5-HT3 antagonist (8mg ondanestrone) and dexamethasone 8 mg over 30 minutes was administered before starting chemotherapy.

Outcome Assessment

Assessment of the response according to the WHO criteria14 was done every 2 cycles with repetition of clinical examination, lab work and routine imaging procedures that had been used to define the extent of the disease at presentation. The response to treatment reported here was the one measured at time of maximum radiological response.

All patients receiving ≥2 cycles and at least one re-evaluation are considered evaluable for response.

Duration of response

Complete response and partial response were calculated from the date of first assessment of response to the date of first progression or last follow up.

Time to progression (TTP)

was calculated from the date of inclusion in the study up to the date of last tumor assessment documenting first progression prior to start of further treatment.

Overall Survival

Survival was calculated from the date of study entry until the last follow up visit or death.

Toxicity

Toxicity was assessed using NCI criteria for common toxicities15 every cycle as well as on follow up.

Dose Modification for myelosuppresion

Table 1: Shows dose modifications for gemcitabine and cisplatin according to Platelet and absolute neutrophil counts (% of Dose to be given)

HEMATOLOGIC TOXICITY				
	Granulocytes			
Platelet Count (/mm3)	>1500	1000-1500	500-1000	<500
>100,000	100	100	75	50
75,000–100,000	75	75	50	0*
50,000- 75,000	50	0	0	0
<50,000	0	0	0	0

**0 indicates treatment should be postponed a week until the counts return to a level at which drugs may be given. If no recovery after 2 weeks despite giving growth factors, the patient was taken off the study.*

Dose modification for renal impairement

For cisplatin: In case of rise of serum creatinine > 1 normal value despite adequate rehydratin, creatinine clearance should be performed before each cycle and dose reduction should be considered.If creatinine clearance is 40-59(ml/min), 50% cisplatin dose at subsequent cycles, and if <40 (ml/min), the patient was taken off the study.

Dose modification for peripheral neuropathy

In case of grade II peripheral neuropathy, cisplatin will be reduced by 25% at subsequent cycles. In case of Grade III peripheral neuropathy, the patient was taken off the study.

Other toxic effects should be managed symptomatically if possible. In case of grade III toxicities chemotherapy would be held for a maximum of two weeks until resolution to grade ≤1, then given with 25% dose reduction. If grade IV toxicity occurs, except anemia and neutropenia, the patient was taken off the study. If a day 8 gemcitabine dose was held or missed, the cycle was continued per protocol with one dose not given. A patient who could not be administered day 8 of treatment for 6 weeks was taken off the study.

Treatment duration and follow up

A thorough examination was done for each patient in all visits, to be supported with radiological and laboratory investigations if needed.

Patients were treated till evidence of disease progression or unacceptable toxicity. Patients achieving CR continued two more cycles after remission with a minimum of 6 cycles and a maximum of 8 cycles. While patients achieving PR or SD continued 2 cycles after maximum response for a minimum of 6 cycles and a maximum of 8 cycles.

For responders who ended their maximum number of cycles, all clinical and radiological assessments were performed every 2-3 months for of all lesions till disease progression.

The patients who failed to respond to the above regimen or were removed from therapy because of progression, further antitunmor therapy was allowed.

Statistical analysis

The data was collected, revised, coded and introduced to a PC. Data was statistically described in terms of range, mean, median, frequencies and relative frequencies. Regarding survival analysis, Kaplan Meier method16 was used .All statistical calculations were done using computer programs Microsoft Excel version 7 and statistical Package for Social Science program version 11 (SPSS package).

Results

This prospective phase II study included 40 female patients with MBC pretreated with anthracyclines as an adjuvant treatment who presented to Radiation Oncology and Nuclear medicine Department, Ain Shams University Hospitals, during the period from December 2006 to June 2009with a median follow up period of 12 months ranging from 3 to 24 months. Patients' accural was done from December 2006 to October 2007.Pateints Characteristics are shown in table (2).

Table 2: Shows Patients' characteristic

Clinicopathological characteristics	Number of patients (percentages)
Age (years): < 40	2 (5%)
Age (years): 40 - 49	17 (42.5%)
Age (years): ≥50	21 (52.5%)
Performance Status (ECOG): 0	15 (37.5%)
Performance Status (ECOG): 1	13 (32.5%)
Performance Status (ECOG): 2	12 (30%)
Menstrual Status:	
Premenopausal	11 (27.5%)
Postmenopausal	29 (72.5%)
Hormone Receptors:	
ER+/ PR+	12 (30%)
ER+/ PR-	15 (37.5%)
ER- /PR+	4 (10%)
ER-/ PR-	9 (22.5%)
Her2 status:	
Positive	18 (45%)
Negative	22 (55%)
Breast cancer phenotypes:	
Her2+	18 (45%)
Her2-/ HR+	17 (42.5%)
Her2-/ HR-	5 (12.5%)
Disease free interval:	
< 2 years	17 (42.5%)
≥ 2 years	23 (57.5%)
Number of metastatic sites:	
1	16 (40%)
2	20 (50%)
≥3	4 (10%)
Metastatic sites:	
Liver	8 (36.36%)
Lung	15 (68.18%)
Others	9 (40.9%)

Regarding previous treatment, 72.5% of patients (29 patients) received FAC regimen as adj. chemotherapy and 27.5% (11 patients) received FEC regimen as adj. chemotherapy, while 77.5% of patients (31 patients) received adj. radiotherapy. Only 32.5% of patients (13 patients) received radiotherapy to metastatic disease before study entry.

About 77.5% of patients (31 patients) received adj. hormonal therapy and 12.5% of patients (5 patients) received hormonal therapy for metastatic disease prior to study entry.

Objective Tumor Response

Out of the forty patients recruited for the study, 38 patients were assessable for response because 2 patients were excluded from the evaluation of response. One patient suffered from sever toxicities (grade IV neutropenia and grade III vomiting) after the first cycle upon which she refused to tolerate further chemotherapy and the other patient suffered from unrelated sudden death (diabetes complication) after the first cycle. The overall objective tumor response (CR+PR) was 57.89%,while the clinical benefit ratio (CR+PR+SD) was 68.42%.Table 3

Table 3: Objective Tumor Response Rate

Response	Number of patients (Percentages)
Complete Response (CR)	2 (5.26%)
Partial Response (PR)	20 (52.63%)
Stationary Disease (SD)	4 (10.53%)
Progressive Disease (PD)	12 (31.58%)

The mean time to response was 2.681 months ± 0.838 month as standard of deviation, the median time to response was 2 ms ranging from 2 to 4 ms with a 95% confidence interval(CI) of (2.34-2.96)ms and the mean cycle to response were 2.563 cycles ±0.791 cycle as standard of deviation, the median cycle to response were 2 cycles ranging from 2 to 4 cycles with a 95% CI of (2.29-2.97) cycles.

The mean duration of response was 9.934 ms ± 4.309 ms as standard of deviation and the median duration of response was 9.5 ms ranging from 3 to 18 ms with a 95% CI of (8.07-11.83) ms.

The mean time to disease progression was 12.63 ms ± 4.091 ms as standard of deviation and the median time to disease progression was 12.5 ms ranging from 5 to 20 ms with a 95% CI of (10.85-14.43) ms.

Table 4: Clinicopathological characteristics among responders

Clinicopathological characteristics	Number of patients (percentages)
Age (years): < 40	1 (4.54%)
Age (years): 40 - 49	11 (50%)
Age (years): > 50	10 (45.46%)
Performance Status (ECOG): 0	9 (40.91%)
Performance Status (ECOG): 1	9 (40.91%)
Performance Status (ECOG): 2	4 (18.18%)
Menstrual Status:	
Premenopausal	7 (31.82%)
Postmenopausal	15 (68.18%)
Hormone Receptors:	
ER+/ PR+	6 (27.27%)
ER+/ PR-	9 (40.91%)
ER- /PR+	2 (9.1%)
ER-/ PR-	5 (22.72%)
Her2 status:	
Positive	8 (36.37%)
Negative	14 (63.64%)
Breast cancer phenotypes:	
Her2+	8 (36.37%)
Her2-/ HR+	10 (45.45%)
Her2-/ HR-	4 (18.18%)
Disease free interval:	
< 2 years	6 (27.27%)
≥ 2 years	16 (72.73%)
Number of metastatic sites:	
1	12 (54.55%)
2	10 (45.45%)
≥3	0 (0%)
Others	9 (40.91%)

Survival

The estimated mean survival was 17.833 ms with a 95% CI of15.459 to 20.207 ms. The estimated median survival was 22 ms with a 95% CI of 16.339 to 27.661 ms. (Figure 1)

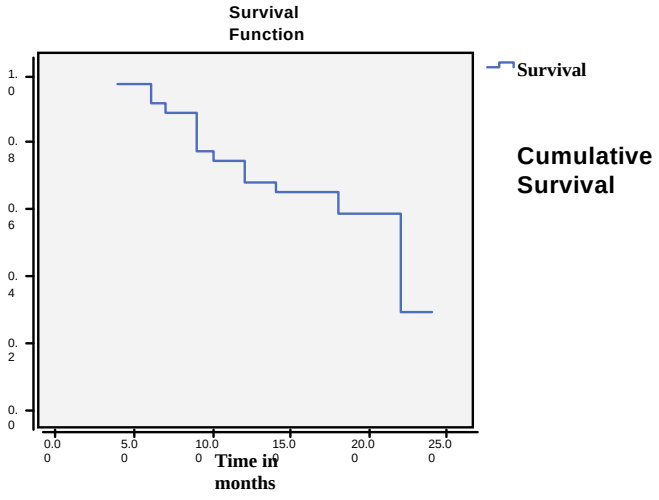

Fig 1: Survival function

From the survival curve, the survival function was estimated at 12 and 24 ms to be 68.52% and 31% respectively.

The estimated mean survival among responders and non-responders were 21.38 & 16.04 ms with a 95% CI of 19.57 to 23.18 & 13.39 to 18.69 ms respectively. The estimated median survival among responders and non-responders were 22 & 16 ms with a 95% CI of 16.84 to 27.15 & 12.89 to 19.10 ms respectively.

Comparative means for survival in relation to different clinicopathological characteristics (cancer phenotypes, performance status, age grouping, menopausal status and responders/non-responders) were done.

The triple negative cancer phenotype and better performance status among the study patients were associated with better survival; but this survival advantage did not reach statistical significance. However, significant survival advantage was observed among responders (P=0.006) Figure (2)

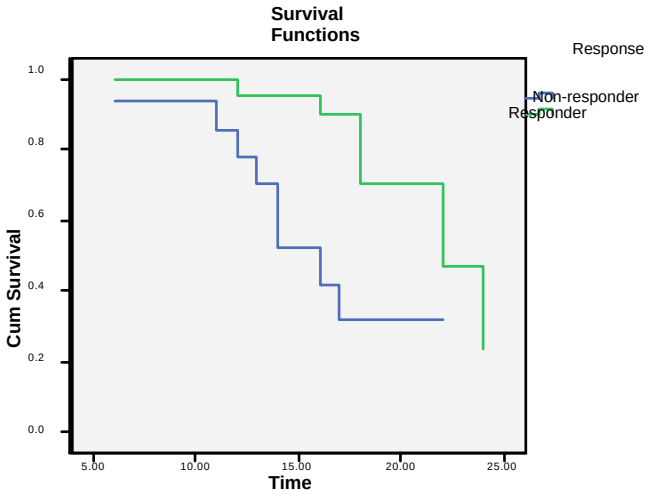

Fig 2: Survival functions in relation to responders/non-responders

Treatment Related Toxicity

The study regimen proved to be quite tolerable with the main hematological toxicities of this protocol were grade III anemia in 10% of patients, grade III/IV neutropenia in 20% of patients and grade III/IV thrombocytopenia in 17.5% of patients. Table (5)

Table 5: Hematological toxicity

Hematological Toxicity		Number of patients (Percentages)
Anemia	Grade I,II	21 (52.5%)
	Grade III,IV	4 (10%)
Neutropenia	Grade I,II	23 (57.5%)
	Grade III,IV	8 (20%)
Thrombocytopenia	Grade I,II	16 (40%)
	Grade III,IV	7 (17.5%)

There were no grade IV non hematological toxicity observed within the study and the only grade III non hematological toxicities recorded in the study were grade III nausea in 25% of patients, grade III vomiting in 17.5% of patients, grade III fatigue in 15% of patients and grade III renal toxicity in 2.5% of patients. Table(6).

Table 6: Most common treatment related non hematological toxicities

Toxicity		Number of patients (Percentages)
Nausea	Grade I,II	30 (75%)
	Grade III	10 (25%)
Vomiting	Grade I,II	23 (57.5%)
	Grade III	7 (17.5%)
Mucositis	Grade I,II	12 (30%)
Diarrhea	Grade I	3 (7.5%)
Alopecia	Grade I	5 (12.5%)
Hepatic toxicity	Grade I	2 (5%)
Renal toxicity	Grade I,II	7 (17.5%)
	Grade III	1 (2.5%)
Febrile neutropenia	Grade III	3 (7.5%)
Fatigue	Grade I,II	16 (40%)
	Grade III	6 (15%)
Neurosensory	Grade I,II	5 (12.5%)

Dose Intensity & Modifications

In total, 173 cycles were administered with a median of 5 cycles per patient (range 1–6). Of all the planned infusions, there were 15 dose reductions (8.67% of cycles) and 10 dose omissions (5.78%) for gemcitabine. Twelve patients (30%) had cycle delays.

Discussion

Sadly MBC is essentially incurable and all the treatment attempts will have more or less a palliative aim to it, which led to the absence of a standardized care for those patients and the subsequent emergence of QOL issues as the essence of MBC patients' care.17

Chemotherapy, targeted therapy and hormonal therapy, in addition to some surgical and radiotherapy maneuvers are the tools used either individually or combined; concomitantly or sequentially to control the metastatic disease according to a wide spectrum of clinical and pathological criteria.

The current phase II prospective single arm single institution trial was conducted to evaluate the usage of gemcitabine plus cisplatin as initial chemotherapy in women with MBC who had received prior anthracyclines in their adj. setting.

Out of the forty patients recruited to the current study, only 38 of them were evaluable for response. Around 5.2% of the patients achieved CR, 52.6% of the patients achieved PR, 10.5% of the patients showed SD and 31.6% of the patients had progressive disease. The overall objective tumor response was 57.9% while the clinical benefit ratio was 68.4%.

The median duration of response was 9.5 ms (95% CI, 8.07 to11.83 ms) and the median time to disease progression was 12.5 ms (95% CI, 10.85 to 14.43 ms). The estimated median survival was 22 ms (95% CI, 16.34 to 27.66 ms). The 1 and 2 years survival probabilities were 68.52% and 31%, respectively.

These results were lower than the results achieved in a multicenter phase II study conducted by Fuentes and colleagues in which 46 patients with assessable MBC with previous exposure to anthracyclines received gemcitabine/cisplatin combination as first line chemotherapy.

Of the 42 evaluable patients, 17% of the patients achieved CR and 64% of the patients achieved PR while 19% of the patients had progressive disease. The overall tumor response was 81% (95% CI 69 to 93%).13

The Median TTP was 14.9 ms (95% CI 0 to 30.2 ms). The median duration of response was 24.2 ms (95% CI 11.2-37.3 ms). The estimated median survival was 27.9 ms (95% CI 23.1–32.7 ms), and the 1 and 2 year survival probabilities were 71.4% and 61.4%, respectively.13

These higher results could be attributed to the better clinico-pathological characteristics of the patients recruited in their study. The patients had an excellent Karnofsky performance status (83% of patients were 90% or above). In addition, only 35% of the patients had visceral metastasis and 40% of the patients had a single site of metastasis. Also only half of the patients received prior adj. anthracycline-based chemotherapy which made them more chemotherapy naive and probably more responsive. In comparison, to our current study where 70% of the patients had an ECOG performance status 0/1 and 80% of the patients had visceral metastasis.13

In another study where twenty two assessable patients for response were given gemcitabine/cisplatin as first line chemotherapy in MBC, 13.6% of the patients achieved CR, 40.9% of the patients achieved PR, 27.2% of the patients had evidence of SD and the remaining 18.2% of the patients had disease progression.The overall objective RR for the patients was 54.5% (95% CI, 38.3 to 76.7%).The overall objective RRs were quite comparable to our current study matched rates.12But their median duration of response being only 5 ms, median TTP of only 8 ms (95% CI, 7.2 to 10.8 ms) and median overall survival being 12.8 ms (95% CI 10.4 to 15.2 ms) were all lower than their matched results in our study12. The superiority of the current results as regard the duration of response and overall survival may be attributed to the higher number of recruited patients (40 patients compared to only 22 patients), also the better patients' clinicopathological characteristics.

In a multivariate analysis of our data a significant survival advantage was observed among responders ,also a trend towards better survival was observed in patients with better ECOG performance status which is an established predictor of response. 19 On the contrary, the menopausal status and the age of the patients recruited in our study did not have a significant effect on our study's survival. Triple negative breast cancer phenotype had a positive implication on survival of our study patients probably due to the platinum component of the protocol. This same observation led to initiation of an ongoing trial that is conducted to evaluate the role of gemcitabine/cisplatin combination as first line therapy in triple negative MBC patients.10

The results of the current study were superior to the results of a recent multi-institutional trial conducted by the US National Cancer Institute. Inspite of being the largest published trial in advanced breast cancer that utilize the combination of cisplatin and gemcitabine in minimally and heavyily treated MBC, the sophistication of the study design and its larger size, it failed to achieve the same responses achieved in the current study as a first line therapy.20
In the NCI study, a total of 136 women were enrolled with similar patients' characteristics in both studies but Her2 status recognition was excluded from the NCI study. The overall RR was 26% for both the heavily pretreated subgroup (95% CI, 16% to 37%) and the minimally
pretreated subgroup (95% CI, 16% to 38%) and the durations of response were 5.3 ms and 5.9 ms, respectively. The median OS rates were 10.8 ms (95% CI, 8.6 to 14.5 ms) in the heavily pretreated study and 13.1 ms (95% CI, 10.9 to 17.6 ms) in the minimally pretreated study. The median PFS rates were 3.8 ms (95% CI, 2.7 to 5.4ms) and 4.2 ms (95% CI, 3.6 to 6.0 ms) in the heavily and minimally pretreated studies, respectively. Interestingly, in a subgroup analysis that was performed for RR; HR- disease was associated with a higher RR that was not observed in the current study instead an increased survival ratio was observed in triple negative responders. 20
In a trial that recruited MBC patients to evaluate the role of gemcitabine/cisplatin as second line chemotherapy. The overall RR was 30% (95% CI, 12 to 53%). The median TTP was 30.6 weeks (95% CI, 12.6 to 44 weeks) and the median survival was 73.2 weeks (95% CI, 47.1 to 93.2 weeks) all are lower than our study's matched data.21 All of these studies and more confirmed the superiority of the usage of the gemcitabine/cisplatin combination as first line therapy in comparison to its usage in minimally or heavily pretreated patients.
The North Central Cancer Treatment Group conducted a phase II study of weekly cisplatin and gemcitabine in a similar population of 58 patients with MBC and reported a RR of 29% and a median TTP of 6 months.22

Another study of 38 patients with prior treatment with anthracyclines and taxanes reported a 40% overall RR with weekly cisplatin and gemcitabine as second-line therapy for MBC. The differences in RRs observed among these studies, including this study are most likely reflecting patient selection as well as differences in dosing and schedule.23

Alternate dosing schedules included weekly lower doses of gemcitabine/cisplatin or a longer time of gemcitabine infusion were proposed by a series of studies. One trial used a weekly regimen of the combination and reported a similar RR to our study with RR of 50% in 30 heavily pretreated patients, but this regimen required modification because of cytopenias.24
Among the forty patients assessable for toxicity, the major hematologic toxicities associated with the current study have been neutropenia and thrombocytopenia, and the major non-hematologic toxicities have been nausea/vomiting and nephrotoxicity.
Our current study was quite comparable to the two first line therapy trials as regard anemia. Ten percent of the patients developed Grade III anemia and none of the patients developed Grade IV anemia. Similarly, Grade III/IV anemia was seen in 9% of the patients in the study conducted by Fuentes. Grade III/IV anemia was seen in only 8% of the patients in Mohran's study. 13,12

Regarding neutropenia, the current study reported a lower incidence of neutropenia than the study conducted by Fuentes but a higher incidence than Mohran's study with 22.5% of patients developing Grade III/IV neutropenia. While in Fuentes study, 36% of patients developed grade III/IV neutropenia. Mohran's study reported a mere 12% of all his patients developing grade III/IV neutropenia. Neutropenic complications were comparable in all three studies.13, 12

The higher percentage of neutropenia found in Fuentes et al, 2006 study could be explained by the higher number of cycles administered in his study.13
On contrary to neutropenia, Fuentes study reported less thrombocytopenia while Mohran's study reported more thrombocytopenia. Seventeen and half % of the current study patients developed Grade III/IV thrombocytopenia. Thrombocytopenia was the major hematologic toxicity observed in Mohran's study with grade III/IV thrombocytopenia in 32% of patients.13,12

About 42.5% of patients developed Grade III nausea/vomiting. Both Fuentes et al., and Mohrans' study recorded similar incidence of grade III nausea/ vomiting 33% and 32%, respectively.13, 12
Twenty percent of the patients suffered from renal toxicity and only one of them developed grade III renal toxicity.While only 12% of Mohran's patients developed renal toxicity.12

The hematological and non hematological toxicities observed in trials using the gemcitabine/cisplatin combination as a second line or salvage therapy for MBC were higher than those observed in our trial.
The toxicities encountered in one trial were higher than our results with grade III/IV neutropenia in 36.4% of the patients compared to 22.5% and grade III/IV anemia in 25.6% compared to 10%.21

Toxicities in the NCI trial were mostly grade III/IV hematological toxicities which were much higher than our recorded toxicities with grades III/IV thrombocytopenia in 71% of patients compared to 17.5%, grade III/IV neutropenia in 66% of patients compared to 22.5% and grade III/IV anemia in 38% of patients compared to 10%. 20 This high incidence of hematological toxicity is most likely the result of using the combination in heavily pretreated MBC patients with depleted bone marrow reserve. Prophylactic growth factors were a required element of the NCI protocol therapy for the heavily pretreated patients20.

Conclusion

In conclusion, the study had found gemcitabine and cisplatin to be an effective and tolerable first-line treatment for MBC patients with impressive results compared to other first line therapies and superiority over the usage of the same combination as second line therapy.

However, because of the small size and patient selection of these studies, the findings should be validated in a larger randomized phase III studies which is also warranted to directly compare this regimen with widely used regimens to substantiate the best options for the treatment of patients in this setting.

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