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Gemcitabine and Carboplatin in Patients with Refractory or Progressive Metastatic Breast Cancer after Treatment

Zedan A[1], Soliman M[2], Sedik MF[1]

[1]Medical Oncology Department, South Egypt Cancer Institute, Assiut University
[2]Faculty of Medicine, Sohag University

Correspondence should be addressed to Mayada Fawzy Sedik at Department of Medical Oncology, South Egypt Cancer Institute, Assiut University, Egypt, mayadaelzohri@yahoo.com

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Abstract

Background, Patients with metastatic breast cancer (MBC) are increasingly exposed to anthracyclines and taxanes either during treatment of primary breast cancer or during initial therapy of metastatic disease. The combination of gemcitabine and carboplatin was therefore investigated as an anthracycline- and taxane-free treatment option; **Methods**, Fifty patients with confirmed metastatic breast cancer previously treated were recruited from medical oncology department at South Egypt Cancer Institute starting from the start of July 2009 till the start of December 2012; the study populations were followed till the start of December 2013 in a multicenter phase II study. Treatment consisted of gemcitabine (1,000 mg/m 2 i.v. on days 1 and 8) and carboplatin (AUC 4 i.v. on day 1) applied every 3 weeks; **Results,** Fifty patients with confirmed MBC were recruited to participate in this study with a treatment protocol approved by the local ethics committee. A total number of 273 cycles were delivered, patients received a median number of 6 and a range of 1-8 cycles, all patients were assessable for response and toxicity. Only three (6%) achieved CR, twenty-seven (54%) achieved PR, seven (14%) had a stable disease while thirteen (26%) had progressive disease. Thirty-seven patients achieved disease control with a rate of 74% DCR (CR+PR+SD). Median overall survival equals 7.72 months and time to progression equals 5.73 months. The predominant toxicity was hematological which occurred in fifteen (30%) patients and only three (6%) had non-hematological toxicity. Fourteen (28%) had both types of toxicity and eighteen (36%) were free. Main hematological toxicity was grade 2 anemia; sixteen (32%) patients , ten (20%) had grade 2 neutropenia while nine (18%) had grade 2 and 3 thrombocytopenia, only one (2%) patient had grade 4 neutropenia and no cases experienced febrile neutropenia. **Conclusions,** Combination chemotherapy with gemcitabine and carboplatin is an effective and generally well-tolerated treatment option for intensively pretreated patients with MBC.

Background

Patients with metastatic breast cancer (MBC) are increasingly exposed to anthracyclines and taxanes either during treatment of primary breast cancer or during initial therapy of metastatic disease. The combination of gemcitabine and carboplatin was therefore investigated as an anthracycline-and taxane-free treatment option [1].

As anthracycline- and also taxane-based regimens have become a standard of care for patients with primary breast cancer in the neoadjuvant and adjuvant setting, the number of patients who have already been exposed to these drugs in the metastatic stage is increasing. Hence, the evaluation of alternative treatment strategies not cross-resistant to anthracyclines or taxanes is mandatory [2]. Gemcitabine is an excellent choice for combination therapy because of its unique mechanism of action and its favorable profile of side effects [3].

Several considerations support the use of gemcitabine and a platinum salt in the salvage treatment of MBC. First, in vitro studies indicate additive or synergistic activity which was most pronounced in platinum-resistant cell lines and was found to be due to an increased formation and an impaired repair of platinum-DNA adducts [4,5]. Second, gemcitabine and carboplatin are usually not included into adjuvant or neoadjuvant chemotherapy. Therefore, resistance to either drug is unlikely to occur. Third, studies investigating the combination have shown minimal overlapping toxicity suggesting an acceptable toxicity profile even in intensively pretreated patients [6]. The present phase II study aimed to evaluate the efficacy and tolerability of gemcitabine applied on days 1 and 8 plus carboplatin applied on day 1 every 3 weeks in previously treated patients with MBC.

Methods

Patient Population: fifty patients with confirmed MBC were recruited to participate in this study with a treatment protocol approved by the local ethics committee.

Inclusion criteria: prior treatment with chemotherapy, hormonal therapy, immunotherapy or local radiotherapy was allowed. The patients were required to have at least one unidimensionally measurable lesion outside a previous radiation port, age ≥ 18 years, ECOG performance state 1 or 2, minimal life expectancy of 12 weeks, adequate hematological, renal, cardiac and hepatic functions. Exclusion criteria: Prior treatment with gemcitabine or platinum agents. Inadequate creatinine clearance (< 60 ml/min), metastases in bone only, symptomatic brain metastases, women who were pregnant, lactating or refuse effective contraception, secondary malignancy, history of another primary malignant disease, active infection, any other concomitant severe clinical condition making implementation of the protocol difficult, administration of other cytotoxic , hormonal agents or radiation therapy was not permitted during the study, with the exception of contraceptives, corticosteroids given as antiemetic treatment, growth factors for neutropenic patients or local palliative radiation.

Patients' Assessment

The patients were evaluated on a regular basis during treatment. The following assessments were performed before each 3-week cycle: physical examination, complete blood count, serum chemistry, and assessment of toxicities. Baseline tumor assessment was performed within 2 weeks of the start of treatment using imaging procedures such as ultrasound, computerized tomography or magnetic resonance imaging. Tumor assessments were repeated after every two cycles of therapy, applying the initially used imaging procedure. In addition, duration of stable disease, time to tumor progression and overall survival were calculated. When clinically indicated, the investigations were repeated during follow-up. Response was defined according to (RECIST) criteria [7] after cycle 2 of treatment. Complete response (CR) and partial response (PR) were re-evaluated after four weeks at the end of the treatment. Patients were reviewed every 2 months with radiological evaluation of disease status when symptoms occurred. CR was defined as loss of disease with no evidence of tumor as indicated by imaging. In patients with PR, the tumor load was reduced by more than 30%. Stable disease (SD) was defined as reduction in tumor size of less than 30% or increase in tumor size of less than 20%. In progressive disease (PD), the tumor size grew more than 20% despite the treatment. The duration of response was calculated from the first demonstration of response to a documented disease progression. Clinical benefit was calculated for responding and stable patients (CR, PR and SD) maintaining the same status for at least six months [7]. The survival was calculated from the initiation of treatment till death by any cause or till the start of December 2013.

Treatment Schedule

Treatment consisted of Gemcitabine 1,000 mg/m2 given as a 30-min infusion on days 1 and 8 and Carboplatin AUC 4 given as a 1-hour infusion on day 1 of a 3-week treatment cycle. Treatment was continued until disease progression or the occurrence of unacceptable toxicity. Dose adjustments were made on the basis of leukocyte and platelet counts on the day of treatment and clinical assessments of non-hematological toxicities.

Dose adjustments were made on the basis of leukocyte and platelet counts on the day of treatment and clinical assessments of non-hematological toxicities. The doses of both drugs were reduced by 25% if the leukocyte count was between 2.5 and 3.0 x 109 /l, while the platelet count exceeded 100 x 109 /l. If the leukocyte count was less than 2.5 x 109 /l or the platelet count less than 100 x109 /l, both drugs were omitted. Doses omitted on day 8 were not replaced and the next cycle was given on time as scheduled but at reduced doses. If any toxicity ≥ grade 3 except nausea/vomiting or alopecia occurred, drug doses were reduced by 50%. If the patient tolerated the dose-modified treatment well, a re-increase of the dose could be attempted in the following cycle. The use of hematopoietic growth factors was allowed in patients with prolonged hematopoietic recovery. Responding patients received a maximum of 6-8 cycles of chemotherapy. [8].

Study endpoints

The primary objective of the study was to determine the objective response rate to the study treatment. Secondary end points included time to progression, survival, and toxicity.

Statistical Analysis

Data obtained from all enrolled evaluable patients was coded and verified by the researcher using SPSS 21.0 Software. PFS was calculated from the start of chemotherapy to the date of progression or last follow up. OS was calculated from the date of study entry to the date of death from any cause. Survival analysis was calculated using Kaplan Meier analysis, the comparison between groups was estimated using log-rank test analysis. Patients who received at least one treatment cycle were evaluable for toxicity, and those who had received at least two treatment cycles or those who progressed after the first cycle were evaluable for response.

Results

Fifty patients with confirmed metastatic breast cancer were recruited from medical oncology department at South Egypt Cancer Institute. Patients had a median age of 45 years and a range of 25 to 67 years, Forty (80%) of the patients had performance state 1, twenty (40%) patients had positive hormonal receptors while twenty-six (52%) had negative receptors and the hormone receptor status was unknown in four (8%) patients. Thirty-six (72%) had grade II tumor

while twelve (24%) had grade III and two (4%) were unknown, Considering number of metastatic site, twelve (24%) had a single metastatic site, eighteen (36%) had two sites and twenty (40%) had three or more sites, Seven (14%) patients had soft tissue metastasis, eleven (22%) had visceral and thirty-two (64%) had both types of metastasis. Twenty-five (50%) patients received both adjuvant chemotherapy and salvage chemotherapy after metastasis, fifteen (30%) received only salvage chemotherapy for metastatic breast cancer and eight (16%) received adjuvant chemotherapy only. Twelve (24%) were exposed to anthracyclins, three (6%) were exposed to taxanes, thirty-four (68%) received both kinds of therapy. Patients' characteristics of the 50 MBC patients included in this study are shown in Table 1 and The Site of Metastasis among the 50 MBC patients in the study are shown in Fig. 1.

Table 1: Patients' characteristics of the 50 MBC patients in the study and different dosing criteria of the chemotherapy regimen used

Variable	
Age in years	
Mean ± SD	44.78 ± 10.6
Median (Range)	45 (25-67)
Performance State	
- 1	40 (80.0%)
- 2	10 (20.0%)
Menopausal State	
- Pre-menopausal	26 (52.0%)
- Post-menopausal	23 (46.0%)
- Male	1 (2.0%)
Hormonal Receptor	
- Positive	20 (40.0%)
- Negative	26 (52.0%)
- Unknown	4 (8.0%)
HER2 Status	
- 0	2 (4.0%)
- +1	1 (2.0%)
- ++2	2 (4.0%)
- Unknown	45 (90.0%)
No. of Cycles	
- ≤3	11 (22.0%)
- ≥3	39 (78.0%)
Treatment Cycle Delay	
- No	27 (54.0%)
- Yes	23 (46.0%)
Gemcitabine Dose	
- Full Dose	47 (84.0%)
- Dose Reduction	3 (6.0%)
Carboplatin Dose	
- Full Dose	42 (84.0%)
- Dose Reduction	8 (16.0%)
Growth Factor Support	
- No	46 (92.0%)
- Yes	4 (8.0%)
Blood Transfusion	
- No	29 (58.0%)
- Yes	21 (42.0%)

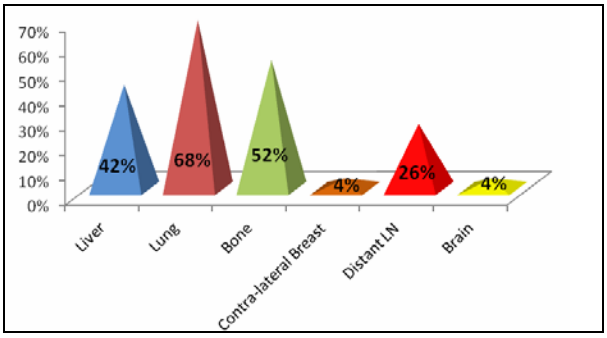

Figure 1: Site of Metastasis among the 50 MBC patients in the study

Treatment Delivery

A total number of 273 cycles were delivered, patients received a median number of 6 and a range of 1-8 cycles, all patients were assessable for response and toxicity. Eleven patients (22%) received three or less cycles while thirty-nine (78%) received more than three cycles. Twenty-seven (54%) patients had treatment cycle delays, three (6%) had dose reductions for Gemcitabine while eight (16%) had dose reductions for Carboplatin. Four (8%) of the patients had growth factor support and blood transfusion was given to twenty-one (42%) patients. Different dosing criteria of the chemotherapy regimen used are shown in Table 1.

Response and Survival

All patients were evaluable for efficacy. Three (6%) patients achieved CR, twenty-seven (54%) achieved PR for an objective response rate (CR + PR) of 60%, seven (14%) had a stable disease. Disease control rate DCR (CR+PR+SD) was 74% (37 patients); this is shown in Fig. 2. A detailed analysis of response of the 50 patients with regard to baseline characteristics was undertaken in Table 2. A higher response rate was observed in patients who received 0 – 2 lines of chemotherapy for MBC, patients with visceral metastasis and patients with negative hormonal receptor status. Moreover, the highest response rate (RR) of 100% (12 out of 12 patients) was in patients who previously received anthracyclins, this RR was also achieved in patients who received neither anthracyclins nor taxanes (1 out of 1).

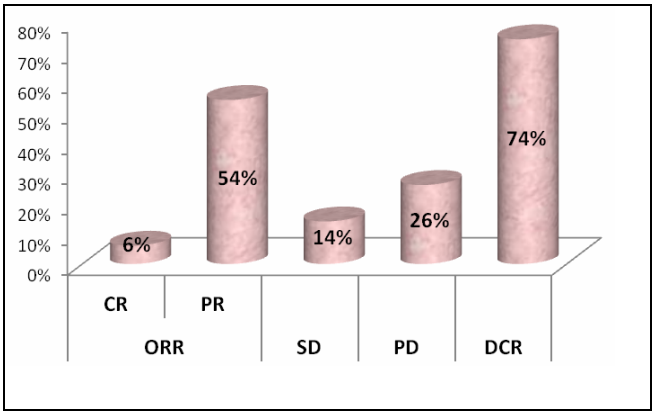

Figure 2: Efficacy of Gemcitabine plus Carboplatin in the 50 MBC patients in the study

Table 2: Response rates of the 50 MBC patients in the study by baseline characteristics

Variable	Total Patients	Overall Response	
		N (%)	**95% CI***
Prior CTs for MBC			
• 0 – 2 (1st & 2nd lines)	47	37 (78.7%)	64.3 - 89.3
• > 2 (Beyond 2nd lines)	3	0 (0%)	----------
Type of Metastasis			
• Soft Tissue (lymph nodes, skin, bone)	7	5 (71.4%)	29.1 - 96.3
• Visceral	11	9 (81.8%)	48.2 - 97.7
• Both	32	23 (71.9%)	53.3 - 86.3
Pre-treatment with Anthracyclines and/or taxane			
• Anthracyclines	12	12 (100%)	----------
• Taxane	3	1 (33.3%)	8.4 - 90.6
• Both	34	23 (67.6%)	49.5 - 82.6
• Neither	1	1 (100%)	----------
Hormonal Receptor Status			
• Positive	20	13 (65.0%)	40.8 - 84.6
• Negative	30	24 (80.0%)	61.4 - 92.3
Previous Hormonal Therapy			
• No	29	23 (79.3%)	60.3 - 90.1
• Yes	21	14 (66.7%)	43.1 - 85.4

*CI = Confidence Interval

Table 3 shows the parameters of time-to-event of the 50 MBC patients included in the study. The median overall survival was 7.72 (95% CI; 5.72-17.08) months, median time to progression was 5.73 (95% CI; 4.23-11.70) months, and the median duration of stable disease was 6.97 (95% CI; 5.51-16.23) months at a median duration of follow up of 7.12 (95% CI; 5.76-9.83) months. The median overall survival and median time to progression are shown in Fig. 3.

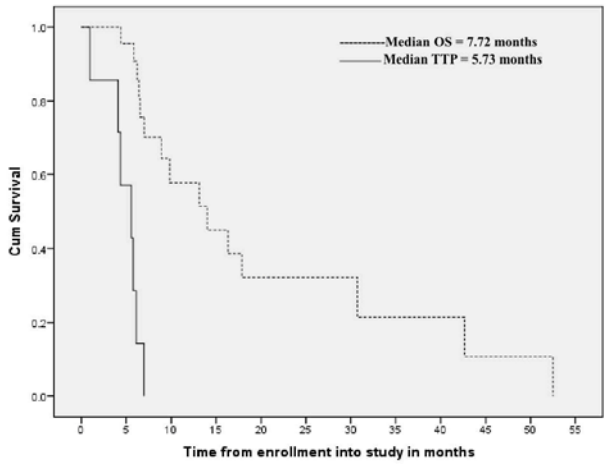

Figure 3: Time to progression (TTP__) and overall survival (OS---) of the 50 MBC patients in the study

Table 3: Time-to-event parameters of the 50 MBC patients in the study

	Median (months)	**95% CI* (months)**
Disease Progression		
• Time to Progression	5.73	4.23-11.70
• Duration of Stable Disease	6.97	5.51-16.23
• Duration of follow-up	7.12	5.76-9.83
Survival		
• Overall survival	7.72	5.72-17.08

*CI = Confidence Interval

The median OS of hormonal positive patients and those who received previous hormonal therapy was 13.1 months while in hormonal negative patients and those who didn't receive hormonal therapy equals 6.4 months (Fig. 4).

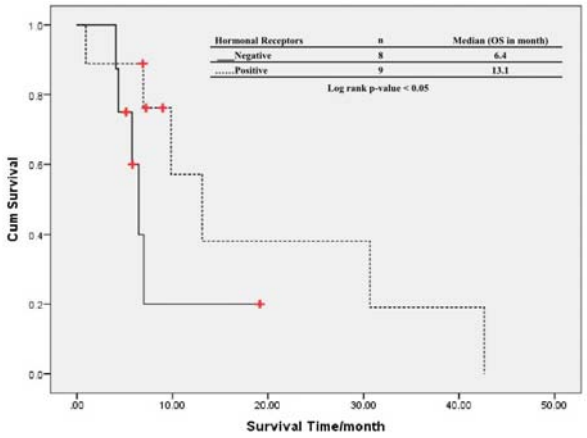

Figure 4: Survival analysis of the 50 MBC patients in the study regarding Hormonal Receptor Status

Toxicity

Figure 5 shows the type of toxicity among the 50 MBC patients in the study. The predominant toxicity was hematological which occurred in fifteen (30%) patients and only three (6%) had non-hematological toxicity. Details of toxicity profile is shown in Table 4 main hematological toxicity was grade 2 anemia; sixteen (32%) patients , ten (20%) had grade 2 neutropenia while nine (18%) had grade 2 and 3 thrombocytopenia, only one (2%) patient had grade 4 neutropenia and no cases experienced febrile neutropenia. The toxicity was observed after the third cycle in most of the patients who experienced hematological toxicity and the blood transfusions were given to anemic and thrombocytopenic patients.

On the other hand concerning non-hematological toxicity the highest number of patients which equals twenty-five 25(50%) had grade 2 nausea/vomiting, fourteen (28%) had grade 1 alopecia , six (12%) had grade 1 raised liver transaminases (ALT-AST) while four (8%) had grade 2, four (8%) had grade 1 bilirubin elevation and three (6%) had grade 2, only three (6%) patients had renal toxicity in the form of grade 1 raised renal toxicity , no grade 3 or 4 non-hematological toxicity was observed.

Table 4: Toxicities of therapy of the 50 MBC patients in the study (number and percentage of patients)

	Total Patients	WHO Grade (N (%))			
		I	II	III	IV
Hematological toxicity					
• Leukopenia	50	9 (18%)	6 (12%)	3 (6%)	0 (0%)
• Neutropenia	50	5 (10%)	10 (20%)	2 (4%)	1 (2%)
• Febrile neutropenia	50	0 (0%)	0 (0%)	0 (0%)	0 (0%)
• Thrombocytopenia	50	5 (10%)	9 (18%)	9 (18%)	0 (0%)
• Anemia	50	7 (14%)	16 (32%)	4 (8%)	0 (0%)
Non-hematological toxicity					
• Alopecia	50	14 (28%)	1 (2%)	0 (0%)	0 (0%)
• Nausea/vomiting	50	25 (50%)	2 (4%)	0 (0%)	0 (0%)
• Asthenia	50	5 (10%)	2 (4%)	0 (0%)	0 (0%)
• Stomatitis	50	7 (14%)	0 (0%)	0 (0%)	0 (0%)
• Neurotoxicity	50	1 (2%)	0 (0%)	0 (0%)	0 (0%)
• AST level	50	6 (12%)	2 (4%)	0 (0%)	0 (0%)
• ALT level	50	6 (12%)	2 (4%)	0 (0%)	0 (0%)
• Bilirubin level	50	4 (8%)	3 (6%)	0 (0%)	0 (0%)
• Creatinine level	50	3 (6%)	0 (0%)	0 (0%)	0 (0%)

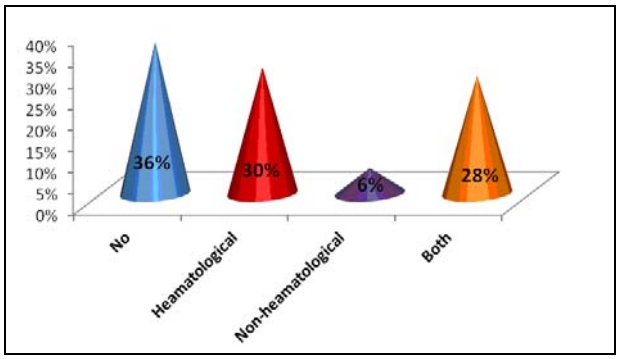

Figure 5: Type of Toxicity among the 50 MBC patients in the study

Discussion

The rational for combining gemcitabine and carboplatin is based on their single-agent activities in metastatic breast cancer, the activity of this combination in other malignancies and on the fact that carboplatin has demonstrated efficacy comparable with cisplatin in several tumor types.

Efficacy and safety of single agent gemcitabine have been reported in patients with locally advanced or metastatic breast cancer, with response rates ranging from 25% to 37% and overall survival ranging from 12 to 21 months depending on its use as first or subsequent line. Gemcitabine has no apparent multidrug resistance, has a mild hematological toxicity profile and is generally well tolerated by patients [9]. Thus, gemcitabine and carboplatin is a logic combination for treatment of this disease. Responding patients received a maximum of 6-8 cycles of chemotherapy, as prior studies had suggested that maximal response would have been achieved by the 4th cycle of chemotherapy and previous randomized studies had suggested similar efficacy between 6 cycles of chemotherapy and more prolonged treatment of up to 12 chemotherapy cycles.

Considering our study the efficacy of gemcitabine plus carboplatin was proven with an overall response rate of 60% (CR 6% + PR 54%) , three (6%) achieved CR, twenty-seven (54%) achieved PR, seven (14%) had a stable disease while thirteen (26%) had progressive disease, thirty seven patients achieved disease control with a disease control rate DCR (CR+PR+SD) of 74%. Regarding the parameters of time-to-event, the median overall survival was 7.72 (95% CI; 5.72-17.08) months, median time to progression was 5.73(95% CI; 4.23-11.70) months, median duration of stable disease is 6.97 (95% CI; 5.51-16.23) months at a median duration of follow up of 7.12 (95% CI; 5.76-9.83) months. The treatment-associated toxicity profile in our study was generally acceptable. The predominant toxicity was hematological which occurred in fifteen (30%) patients and only three (6%) had non-hematological toxicity. Fourteen (28%) had both types of toxicity and eighteen (36%) were free, main hematological toxicity was grade 2 anemia in (32%) of patients, grade 2 neutropenia in (20%), grade 4 neutropenia in (2%) of patients and no cases experienced febrile neutropenia, and grade 2 and 3 thrombocytopenia each in (18%) of patients. Twenty-seven (54%) patients had dose delay while twenty-three (46%) did not have any dose delay. There were no serious infections, bleeding episodes, or treatment-related deaths. Considering dose reduction for Gemcitabine forty-seven (94%) had full dose and three (6%) had dose reduction. Considering Carboplatin, forty-two (84%) had full dose while eight (16%) had dose reduction. Only four (8%) of the patients had growth factor support while the rest forty-six (92%) did not receive. Blood transfusion was given to twenty-one (42%) patients and twenty-nine (58%) did not receive. Because all our patients had multiple previous treatments, these observations could explain the high hematological toxicity.

These results compared favorably with those published by other investigators evaluating gemcitabine-carboplatin regimen. There was a

difference with regard to efficacy parameters in terms of response rate in our study which reached 60% compared to Laessig D et al., 2007 (31%) [10], and Nasr FL et al., 2004 (30%) [11], while ORR reported by Latini et al., 2003 (69%) [12], and Nagourney et al., 2004 (50%) [13] were close to that reported by our study.

The difference in overall response rate between our study and the previously mentioned studies could be explained by the fact that in our study response rates were estimated using RECIST criteria while the previously mentioned studies used WHO criteria so many patients that would have a stable disease according to WHO had a PR which increased the overall response rate (60%) and disease control rate (74%) in our study.

Regarding the parameters of time-to-event, the median overall survival reached 7.72(95% CI; 5.72-17.08) months which was less than that reported by to Laessig D et al., 2007 (13.2 months) [10], median time to progression is 5.73(95% CI; 4.23-11.70) months, median duration of stable disease is 6.97(95% CI; 5.51-16.23) month which was comparable to those reported by Laessig D et al., 2007 (the median duration of most responses and disease stabilizations was 3.3 and 6.8 months, respectively and the median time to progression was 5.3 months) [10].

Regarding the difference in overall survival it was noticed that the median OS of hormonal positive patients (those who received previous hormonal therapy and continued on second line hormonal therapy following chemotherapy) was 13.1 months (nearly equal to that reported by Laessig D et al., 2007 [10]) while in hormonal negative patients (those who didn't receive hormonal therapy and were put under follow up following chemotherapy) equals 6.4 months, so initially there was a good response in hormonal negative patients but after finishing chemotherapy there was rapid deterioration attributed to the aggressive course of the disease.

Most of the patients included in the study performed by Laessig D et al., 2007 [10] were hormonal positive (a total of 39 patients, 30 (77%) were hormonal positive, 8 (21%) were hormonal negative and 1 (2%) unknown receptors), while in our study a total of fifty patients twenty (40%) patients had positive hormonal receptors while twenty-two (52%) had negative receptors and four (8%) were unknown.

Recently Chan D et al., 2010 [14] investigated the combination of gemcitabine and carboplatin in MBC with prior exposure to both anthracyclines and taxanes. Treatment consisted of gemcitabine (1,000 mg/m2 I.V on days 1 and 8) and carboplatin (AUC 5 I.V on day 1) administered every 3 weeks. Results 41 patients were recruited. Objective response rate was 39% including 1 complete response (2%) and 15 partial responses (37%). Twelve patients (29%) had stable disease. Median time to progression was 4.6 months (95% CI 3.3-5.9 months) and median overall survival 10.5 months (95% CI 7.6-13.4 months). Grade 3 & 4 hematological toxicities included neutropenia (58%), febrile neutropenia (15%), anemia (12%) and thrombocytopenia (49%), including 7% who required platelet transfusions. Non-hematological toxicity was rarely severe. 56% of patients required at least one dose reduction; the mean relative dose intensity for gemcitabine and carboplatin were 0.82 (range 0.5-1.0) and 0.95 (range 0.75-1.00) respectively, with no difference in dose intensity between responders and non-responders. Gemcitabine combined with carboplatin has promising efficacy in MBC with prior treatment with anthracyclines and taxanes but has significant hematological toxicities requiring dose modifications. The regimen may be modified to gemcitabine 800 mg/m2.

Also Nelli F et al., 2013 [15] evaluated the efficacy of gemcitabine and carboplatin for patients affected by pretreated metastatic breast cancer. A subgroup analysis was performed to evaluate the predictive value of immunohistochemically defined breast cancer subtypes. Forty-two patients were registered. Disease control was 58%, with a median time-to-progression (TTP) of 7 months (range 1-12) and a median overall survival of 10.5 months (range 1-34). Patients were grouped as triple negative (ER and PR negative, HER-2 negative), HER-2 (HER-2 positive, ER and PR negative), luminal B (ER and/or PR positive and either HER-2 positive and/or high Ki67), and luminal A (ER and/or PR positive and HER-2 negative and low Ki67). For luminal A patients, disease control was lower (luminal A 34 vs. others 67%; P = 0.02), TTP was shorter (luminal A 2.4 months vs. others 6.3 months, P = 0.015), and overall survival was shorter (luminal A 7.5 months vs. others 11.7 months, P = 0.034) than for other subtypes. Gemcitabine and carboplatin are effective for pretreated patients with metastatic breast cancer. Luminal A subtype seems to fare poorly compared with other subtypes. Specific difference in gene expression might account for the different outcome.

Compared to this study categorizing patients into these subgroups was not applicable that's because the detection of hormonal and her2/neu receptors were done at the time of initial diagnosis which was years away from the time of enrollment in this study so retrieving the blocks for immunohistochemical studies was difficult in most of the cases thus making the analysis of data unreliable.

The observed activity and tolerable toxicity profile would support further evaluation of this carboplatin plus gemcitabine schedule. Gemcitabine-based chemotherapy appears to be a notable treatment option for pretreated patients with MBC.

Conclusion

The combination of gemcitabine plus carboplatin is a generally well-tolerated and effective regimen that provided sustained disease control in breast cancer patients. Specifically after previous exposure to anthracyclines and/or the taxanes (ORR 60% DCR 74%), this regimen can be considered as an active treatment option which offers a favorable balance between efficacy and tolerability. This combination is easy to administer as an outpatient program.

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