First-line therapy with Docetaxel and Gemcitabine in chemotherapy naive metastatic breast cancer: A Phase II Study

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Abstract

Purpose: This phase II study of biweekly docetaxel and gemcitabine was performed to investigate the efficacy and safety of this combination in treatment of patients with metastatic breast cancer.

Patients and Methods: This study included 40 patients with previously untreated, stage IV breast cancer, the period between October 2008 and July 2011. Therapy consisted of 50 mg/m2 of docetaxel and 1500 mg/m2 gemcitabine, both administered on days 1 and 15 every 4 weeks.

Results: A total of 40 patients were evaluated by intention-to-treat analysis for efficacy and safety. The overall response rate (ORR) was 65% (complete and partial response, 10 and 55%, respectively). Non-hematological toxicity was more common than hematological toxicity, with alopecia and asthenia were the most frequently reported adverse events. Severe hematological toxicity was rare.

Conclusions: Biweekly docetaxel plus gemcitabine appears to be very effective and fairly well-tolerated regimen for the treatment of patients with metastatic breast cancer.

No authors report any conflict of interest.
A written informed consent was obtained from each patient in accordance with institutional and government guidelines.

Introduction

In most developed countries, breast cancer is second only to lung cancer as the most common cause of cancer-related death in women [1]; therefore, it represents a serious health-care problem. Systemic therapy for patients with metastatic breast cancer (MBC) consists of hormonal therapy and cytotoxic chemotherapy. Anthracyclines(doxorubicin and epirubicin) can yield response rates of around 20- 40% in MBC patients when used as single agents, and up to 60% when combined with other cytotoxic drugs [2]. However, the efficacy achieved with anthracyclines comes at the cost of high toxicity. Recently, new cytotoxic drugs with high activity were emerged, such as taxanes (paclitaxel and docetaxel), vinorelbine, gemcitabine, and capecitabine .These drugs have raised the hopes of patients with MBC to experience higher efficacy with tolerable toxicity. Many studies showed that combination chemotherapy may be more effective than single-agent therapy [3, 4].Development of new agents and/or drug combinations with a superior therapeutic index remains a principal goal of investigational efforts. Gemcitabine (difluorodeoxycytidine, dFdC) possesses a broad range of activity against various solid tumors including advanced breast cancer patients (ABC), and is characterized by a favorable toxicity profile [5]. Gemcitabine has a complex mechanism of action that may involve incorporation into replicating DNA and termination of DNA chain elongation. It also has a favorable safety profile, with myelosuppression, mild nausea and lethargy as its major toxicities [6]. Gemcitabine can be used as single agent or in combination regimens, it showed an objective response rate(ORR) of 25–46% in ABC patients, depending on whether this drug was used as first- or second-line treatment [7]. Docetaxel inhibits microtubule depolymerization with high percentage and more prolonged duration and causes cell cycle arrest in the radiosensitive G2-M phase [8]. And it aborts mitosis and causes cell death in the radioresistant S-phase, thereby exerting its cytotoxic effect at more than one point in the cell cycle [9]. The two drugs have distinct mechanisms of action and, with the exception of neutropenia, non-overlapping toxicities [6].The combination of docetaxel with gemcitabine has been tested, both in chemonaive and pretreated patients [10]. In a study conducted by Ricotti and his co-workers found that both agents are active and it was seen that the sequence docetaxel-gemcitabine was characterized by a synergic effect, whereas the inverse sequence or simultaneous exposure to the two drugs induced an antagonistic effect. It was also observed that a 24-h exposure to docetaxel determined a cell cycle block in G2-M phase and that after 24 hours, the majority of cells had moved into G1-S, which is the most sensitive phase to the action of gemcitabine. Furthermore, the percentage of cells in apoptosis increased considerably after sequential docetaxel-gemcitabine treatment [11]. Based on the previously mentioned data we conducted the present study to evaluate the efficacy and toxicity of a regimen containing gemcitabine plus docetaxel in previously untreated patients with MBC. In order to minimize acute toxicities especially myelosuppression, we used a biweekly administration schedule.

Materials and Methods

Patient Population and Eligibility Criteria

Eligible patients had to be female, aged 18-70 years, and had histologic or cytologic diagnosis of breast carcinoma and stage IV disease. Prior chemotherapy was not allowed. Patients could not have received previous therapy with gemcitabine or a taxane. Other inclusion criteria included: World Health Organization (WHO) performance status ≤ 2, and estimated life expectancy of at least 12 weeks. Patients were required to have at least one bidimensionally measurable lesion. Prior radiation was permitted only if measurable disease was outside a previously irradiated area, if radiotherapy was not given to more than 50% of bone marrow volume, and if it was terminated at least 4 weeks prior to enrollment. Adequate hematological, renal and hepatic function was essential for all patients; where leucocytic count ≥4.000/mm3, platelet count ≥100.000/mm3, hemoglobin >9 g/dl, serum creatinine <1.4 mg/dl, serum bilirubin ≤1.5 mg/dl, serum transaminase ≤3×ULN in cases without liver metastases and ≤ 5×ULN in cases with liver metastases.

Exclusion criteria included:

active severe infection, severe heart disease, active concomitant malignancy (except in situ carcinoma of the cervix or adequately treated basal cell carcinoma of the skin), brain metastases, peripheral neuropathy and bone metastases as the only site of disease.

The study protocol was approved by the institution Ethics Committee and it conforms to the provisions of the Declaration of Helsinki (as revised in Seoul 2008).

Treatment plan

Forty patients with MBC received docetaxel 50 mg/m2 followed by gemcitabine 1500 mg/m2 both were given on days 1 and 15 to be repeated every 4 weeks.

Chemotherapy

Patients received docetaxel 50mg/m 2 diluted in 250 c.c normal saline 0.9% over 1hour intravenous (i.v) infusion on days 1 and 15, followed by gemcitabine 1500mg/m 2 diluted in 250c.c saline over 30 minutes i.v infusion on days 1 and 15. To avoid fluid retention and/or anaphylactic reactions, all patients must receive standard premedication with i.v. dexamethasone (20 mg), antihistamine, ranitidine Hcl (Zantac) and antiemetic treatment (ondansetron 16mg or granisetron 3mg) 1 hour before the start of therapy with docetaxel; dexamethasone must be taken the night before, morning of, and evening after treatment .Treatment was recycled every 4 weeks and to be continued in patients exhibiting a complete response (CR) or partial response (PR) for a maximum 8 cycles. Chemotherapy was stopped in case of progression, patient refusal and unacceptable toxicity. Patients who had received at least one cycle of chemotherapy were evaluated for toxicity and at least two cycles for efficacy.

Granulocyte colony-stimulating factor (G-CSF) was used either curatively or as prophylaxis against febrile neutropenia.

Pre-treatment assessment and Post-treatment Reassessment

Each patient must have the following assessment tests before being enrolled into the study:

Full medical history and clinical examination, baseline tests included a full blood count, serum biochemistry (urea, creatinine and electrolytes, liver function tests, calcium).Staging procedure for all patients included CT scan of the chest and pelviabdomen with contrast. CT scan and/or MRI of brain or a bone scan were also done. Patients were followed every 2 cycles of chemotherapy to document response (regression, stable disease or progression). Patients were followed after completion of the course of treatment monthly until disease progression or death. Radiological responses were documented by a CT scan and/or MRI. Treatment toxicity was classified according to the criteria of the World Health Organization (WHO) [12]. Tumor response was evaluated every two cycles of chemotherapy using the same evaluation method and it was classified according to the WHO criteria. A complete response (CR) was defined as the disappearance of any evidence of tumors for at least 4 weeks. A partial response (PR) was defined as ≥ 50% reduction in the sum of the products of the greatest perpendicular diameters of all lesions for at least 4 weeks. Stable disease (SD) was defined as <50% reduction or <25% increase in the products of the greatest perpendicular diameters of all lesions without any evidence of new lesions. Progressive disease (PD) was defined as an increase of ≥25% or the appearance of new lesions.

Dose adjustments for toxicity

Dose adjustments during treatment were made based on Absolute Neutrophil Count (ANC) and platelet counts performed within 24 hours prior to the start of therapy and clinical assessment of nonhematologic toxicities. The day-1 dose of each subsequent cycle depended on the toxicity seen in the previous cycle. The treatment was delayed until the ANC returned to 1500 and the platelet count to 100.000. Otherwise, full doses of both drugs were given, except in patients with WHO grade 4 neutropenia lasting >1 week, grade 4 neutropenia associated with fever ≥38.5°C, or grade 4 thrombocytopenia. In these circumstances, after recovery, the day 1 and 15 doses of both drugs were given at 75% of the dose given on day 1 of the last cycle. The observed nonhematologic toxicities (except alopecia and vomiting) had to return to WHO grade 0 to 1, or baseline conditions, before resuming injections of both drugs. Doses in subsequent cycles were reduced to 75% or held for any grade 3 nonhematologic toxicity (except nausea/vomiting and alopecia), and were reduced to 50% or held for any grade 4 nonhematologic toxicity. Patients were withdrawn from the study after 3 weeks of treatment delay due to any toxicity. If serum bilirubin was increased to >1.5 ×ULN or AST/ALT increased to >3 ×ULN in patients without liver metastasis and >5.0×ULN in patients with liver metastasis at the start of the next cycle then the cycle could not begin until serum bilirubin returned to ≤1.5 ×ULN and AST/ALT returned to ≤3 ×ULN in patients without liver metastasis and ≤5.0 × ULN in patients with liver metastasis. If the values did not return to these limits within 42 days from Day 1 of the current cycle then the patient was discontinued from the study. The doses of gemcitabine and docetaxel were reduced by 20% in the subsequent cycle(s) if serum bilirubin was increased 2-folds or AST/ALT was increased 5-folds relative to baseline at any time during the cycle. Dose adjustments on Day 15 for hepatic toxicity had no effect on dosing in subsequent cycles. In the case of grade 2 arthralgia and/or myalgia, asthenia, or fatigue, the gemcitabine and docetaxel doses were reduced by 20% in all subsequent cycles. Treatment was discontinued if these toxicities were of grade 4.

Data analysis

Descriptive statistics were used to characterize study subjects and response to treatment. The primary end point of the study was the response rate. The toxicity was the secondary end point which was assessed as mentioned above using the (WHO criteria).Survival curves were established with the Kaplan-Meier method [13]. Overall survival was calculated from the date of starting treatment to the date of death or last follow-up; while Time to Tumor Progression (TTP) was calculated from the date of starting treatment to the date of evidence of progression, disease progression, or last contact. The data were analyzed with Graphpad prism software version 4.03.

Results

Patient Characteristics

Forty patients with MBC were enrolled in the study from October 2008 to July 2011in Ain Shams University Hospitals and other private centers. A summary of the patient characteristics is shown in Table 1. Median age was 54 years (range 31–72). Hepatic and pulmonary metastases were present in a large proportion of patients (56%). All patients were eligible and assessable for response and toxicity.

Table 1. Baseline characteristics of patients (n = 40)

Characteristics	n (%)
Median age, years (range)	*54 (31-72)*
WHO performance status	
0	*39(98)*
1	*1 (3)*
Menopausal status	
Premenopause	*18(45)*
Perimenopause	*2(5)*
Postmenopause	*20(50)*
Location of Metastases	
Pulmonary	*11(28)*
Hepatic	*11(28)*
Nodes	*9(23)*
Bone	*7(18)*
Skin/soft tissue	*2(5)*
Histology	
IDC	*36(90)*
ILC	*4(10)*
Hormonal Receptor Status	
Positive	*27(68)*
Negative	*13(33)*
Her2/neu status	
Overexpressed	*9(23)*
Non-overexpressed	*31(78)*

Response

A total of 204 cycles of chemotherapy were given for the patients in this study, with a median of 5 cycles per patient. Complete response occurred in 4(10%) patients; while partial response occurred in 22(55%) patients. Therefore, overall objective response rate was recorded in 26(65%) patients [95% confidence interval (CI) 56% - 80%]. Stable disease occurred in 8(20%) patients. Progressive disease occurred in 6(15%) patients (Table 2).

Table2. Response Rates

Response	n,%
Complete response(CR)	*4(10%)*
Partial response(PR)	*22(55%)*
Overall response(ORR)	*26(65%)*
Stable disease(SD)	*8(20%)*
Progressive disease(PD)	*6(15%)*

After a median follow up time of 14.8months (range 4-33 months), the median overall survival time was 14 months (95% CI, 4.5-17 months). While median Time to Tumor Progression (TTP) was 7 months (95% CI, 4.7-10 months) for patients who achieved initial response (CR, PR and SD). (Figures1and 2). The most common sites of disease progression were liver and lung, which were the most commonly involved sites at baseline.

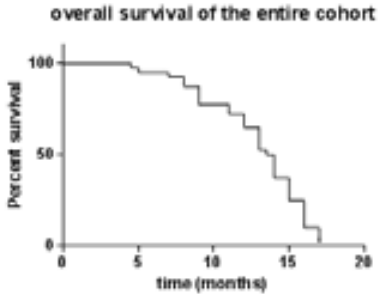

Fig 1. Overall Survival (OS)

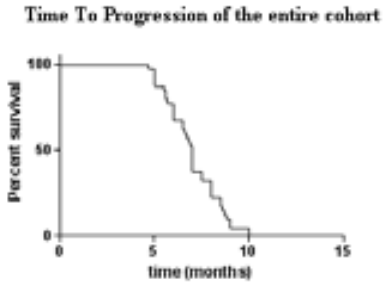

Fig 2. Time to Tumor Progression (TTP)

Toxicity

Toxicity was assessed in 40 patients (Table 3). Asthenia was the most common grade 3/4 non-hematological toxicity which occurred in 8 (20%) patients, followed by nail disorders which occurred in 7 (18%) patients. Only 1 (2.5%) patient developed grade 3/4 anemia, and 2 (5%) patients developed grade 3/4 neutropenia, however, no febrile neutropenia was observed. No treatment related deaths (neither due to sepsis nor bleeding) were reported in the study.

Table 3. Hematological and non-hematological toxicities (n = 40)

Toxicity	Grade 1/2		Grade 3/4	
	n	*%*	*n*	*%*
I- Hematological				
Anemia	*2*	*5*	*1*	*2.5*
Leucopenia	*20*	*50*		
Neutropenia	*20*	*50*	*2*	*5*
Thrombocytopenia	*4*	*10*	*0*	
II- Nonhematological				
Alopecia	*40*	*100*	*0*	
Asthenia	*24*	*60*	*8*	*20*
Conjunctivitis	*10*	*25*	*2*	*5*
Cutaneous	*20*	*50*	*6*	*15*
Diarrhea	*16*	*40*	*2*	*5*
Hypersensitivity	*4*	*10*	*0*	
Infection	*6*	*15*	*1*	*2.5*
Nail disorder	*22*	*55*	*7*	*18*
Nausea/Vomiting	*16*	*40*	*0*	
Paresthesia	*21*	*43*	*2*	*5*
Peripheral edema	*9*	*23*	*0*	
Stomatitis	*14*	*35*	*2*	*5*

Discussion

Metastatic breast cancer (MBC) remains essentially an incurable disease even with the availability of different chemotherapeutic and biological agents with < 10% of patients disease-free beyond 5 years. Treatment of patients with MBC using chemotherapy is mainly to relieve disease-related symptoms, to improve quality of life and to prolong survival [14]. It is wise to try to achieve a significant symptom improvement beside high response rates but not at the expense of substantial adverse effects. The rationale for combining gemcitabine and docetaxel included: (i) their potent mechanism of action with different intracellular targets; (ii) both drugs have a high level of single activity in MBC[15,16]; and (iii) promising and encouraging results of some phase I/II trials evaluating this combination as first and second-line therapy in ABC[17, 18]. The results of our study showed that the combination of docetaxel and gemcitabine is a highly active and well tolerated regimen in first-line therapy of naïve patients with MBC.

In the current study, ORR was recorded in 26(65%) patients [95% confidence interval (CI) 56% - 80%]; where 4(10%) patients attained CR; 22(55%) patients attained PR. Stable disease (SD) occurred in 8(20%) patients and 6(15%) patients had PD. These response rates are almost similar to that reported in the study conducted by Kornek et al [19] who evaluated 52 patients with MBC; they reported that ORR was 61% for patients who had not received prior chemotherapy for metastatic disease [95% confidence interval, 43.4–75.9%], including 4 CR (10.5%) and 19 PR (50%); 9 patients (24%) had SD, and 5 (13%) PD. While in the study conducted by Laufman and his co-workers [20] who enrolled 39 patients with MBC and they used monthly docetaxel combined with weekly gemcitabine; they reported that ORR was 79% (31 of 39, 95% CI. 63%-91%) which is higher than our results; 2 (5%) cases attained CR and 29 (74%) patients had PR. While our results were superior to that reported by Chan et al [21] who showed that ORR in the arm of gemcitabine combine with docetaxel was 32% (49 of 153, 95% CI 24.6 to 39.4%); 7(5%) patients attained CR and 41(43%) patients had PR. In the present study median follow up time was 14.8 months (range 4-33 months) and the median OS time was 14 months (95% CI, 4.5-17 months), while the median TTP was 7 months (95% CI, 4.7-10 months). Kornek et al [19] reported similar results in their study, where the median follow up time was 15 months (range, 8–24 months), and the median survival duration was > 15 months (range, 1.8 – 23+ months), while the median TTP was 8.5 months (range, 2 - 19+ months) ;while Laufman et al [20] showed that after a median follow up time of 24.9 months (range, 5.7 to 34.2+ months), the median OS was much higher than that reported in our study and that reported by Kornek et al [19]; while Chan et al [21] had reported that the median OS was 19 months (95% CI, 15.57 to 23.59 months).

The toxic effects of the combination chemotherapy in the present study were manageable and consisted mainly of non-hematological toxicities. Alopecia was the most prominent toxicity of this combination of drugs and it occurred as a grade 1/2 in all of the enrolled patients 40(100%) patients, followed by grade 1/2 asthenia which occurred in 24 (60%) patients and as a grade3/4 in 8(20%) patients, while grade 1/2 nail disorders had reported in 22 (55%) patients and as a grade 3/4 in 7(18%) patients. As regards the hematological toxicities in the current study, myelosuppression was occurred in the form of grade 1/2 neutropenia 20(50%) patients and 4(10%) patients had developed grade 1/2 thrombocytopenia, while grade 3/4 neutropenia had been reported in 2(5%) patients and grade 3/4 anemia in only one (2.5%) patient. Some cases needed to use G-CSF as a therapeutic maneuver for neutropenia and despite the reported neutropenia there was no reported cases of febrile neutropenia. While Kornek and his co-workers [19] documented that myelosuppression was the most common adverse reaction, as grade 1/2 anemia had occurred in 61% of the 52 enrolled patients and grade 1/2 neutropenia had occurred in 50% of their patients, while the most common non-hematological toxicity in their study was nausea and vomiting which had occurred as grade 1/2 in 58% patients followed by grade 1/2 alopecia in 37% of the enrolled patients. In the study conducted by Chan et al [21], hematological toxicities were severe as grade 1/2 anemia occurred in 93% of the cases, 84% of the patients had developed grade 3/4 neutropenia, while alopecia in 68% of their patients and grade 1/2 nausea and vomiting in 46% of their studied patients.

Conclusion

In conclusion, gemcitabine in combination with docetaxel (given on days 1 and 15) has demonstrated an acceptable activity as well as a well tolerable safety profile. Further evaluation of this regimen is warranted in the treatment of patients who are chemotherapy naïve metastatic breast cancer as a first line.

References

1. Jemal A, Thomas A, Murray T, Thun M (2002): Cancer statistics, 2002. CA Cancer J Clin, 52:23-47.
2. Mouridsen HT: Systemic therapy of advanced breast cancer (1992). Drugs, (Suppl 4):17
3. O'Shaughnessy J, Miles D, Vukelja S, Moiseyenko V, Ayoub JP, Cervantes G et al (2002). Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: Phase III trial results. J Clin Oncol, 20:2812-2823
4. Fossati R, Confalonieri C, Torri V, Ghislandi E, Penna A, Pistotti V et al (1998). Cytotoxic and hormonal treatment for metastatic breast cancer: A systematic review of published randomized trials involving 31,510 women. J Clin Oncol, 16:3439-3460
5. Haider K, Kornek G. V, Kwasny W, Weinländer G, Valencak J, Lang F et al (1999). Treatment of advanced breast cancer with gemcitabine and vinorelbine plus human granulocyte colony-stimulating factor. Breast Cancer Res Treat., 55: 203-211
6. Rischin D, Boyer M, Smith J, Millward M, Michael M, Bishop J et al (2000).A phase I trial of docetaxel and gemcitabine in patients with advanced cancer. Annals of Oncology,11: 421-426
7. Spielmann M, Llombart-Cussac A, Kalla S, Espie M, Namer M, Ferrero JM, et al (2001). Single-agent gemcitabine is active in previously treated metastatic breast cancer. Oncology, 60: 303-307
8. Wirth LJ, Lucca J, Ostle P r, Fidias P, Lynch C, Jänne PA, et al (2003). A phase I study induction docetaxel and carboplatin followed by weekly docetaxel and carboplatin with concurrent radiotherapy, then surgery in stage III non small cell lung cancer. Clin Cancer Res 9: 1698-704.
9. Valero V, Jones SE, Von Hoff DD, Booser DJ, Mennel RG, Randin PM, et al (1998). A phase II study of docetaxel in patients with paclitaxel-resistant metastatic breast cancer. J Clin Oncol. 16: 3362-68.
10. Mavroudis D, Kouroussis Ch, Malamos N et al (1998). A phase II trial of docetaxel and gemcitabine as second-line treatment in metastatic breast cancer. Proc Am Soc Clin Oncol ; 17:158a
11. Ricotti L, Tesei A, De Paola F et al (2003). In vitro schedule-dependent interaction between docetaxel and gemcitabine in human gastric cancer cell

lines. Clin Cancer Res 9: 900–905.

12. Miller AB, Hoogstraten B, Staquet M, Winkler A (1981). Reporting results of cancer treatment. Cancer 47:207-214.
13. Kaplan E and Meier P (1958): Nonparametric estimation from incomplete observations. J Am Stat Assoc 53, 457-481.
14. Amadori D. and Cecconetto L (2006).Gemcitabine and taxanes in metastatic breast cancer. Annals of Oncology 17 (Supplement 5): v173–v176.
15. Spielmann M, Llombart-Cussac A, Kalla S, Espie M, Namer M, Ferrero JM, et al (2001). Single-agent gemcitabine is active in previously treated metastatic breast cancer. Oncology, 60: 303–307.
16. Nabholtz, JM (1999). The role of taxanes in the management of breast cancer. Semin. Oncol, 26 (Suppl. 8): 1-3.
17. Mavroudis,D, Malamos N, Alexopoulus A, Kourousis C, Agelaki S, Sarra E et al (1999). Salvage therapy in anthracycline pretreated metastatic breast cancer patients with docetaxel and gemcitabine: a multicenter Phase II trial. Ann. Oncol., 10: 211–215.
18. Frasci G, Comella P, D'Aiouto, G, Thomas R, Capasso I, Elmo,M, et al (2000). Weekly docetaxel plus gemcitabine or vinorelbine in refractory advanced breast cancer patients: a parallel dose-finding study. Ann. Oncol., 11:367–371.
19. Kornek GV, Haider K, Kwasny W, Raderer M, Schüll B, Payrits T et al (2002). Treatment of Advanced Breast Cancer with Docetaxel and Gemcitabine with and without Human Granulocyte Colony-stimulating Factor. Clin Cancer Res 8:1051-1056.
20. Laufman LR ,Spiridonidis CH, Pritchard J, Roach R, Zangmeister J, Larrimer N et al (2001). Monthly docetaxel and weekly gemcitabine in metastatic breast cancer: A phase II trial. Annals of Oncology 12 1259-1264.
21. Chan S, Romieu G, Huober J, Delozier T, Tubiana-Hulin M , Schneeweiss A et al (2009). Phase III Study of Gemcitabine Plus Docetaxel Compared With Capecitabine Plus Docetaxel for Anthracycline-Pretreated Patients with Metastatic Breast Cancer. J Clin Oncol 27:1753-1760