Gemcitabine Plus Doxorubicin as First-Line Treatment in Advanced or Metastatic Breast Cancer (MBC), A Phase II Study

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ABSTRACT

Introduction: Doxorubicin and Gemcitabine have promising antineoplastic activity and manageable toxicity as a single agent in the treatment of patients (pts) with advanced breast cancer.

Aim of the Study: This study evaluated the efficacy and toxicity of the combination of gemcitabine plus doxorubicin as first-line treatment of advanced or MBC patients.

Patients and Methods: Patients with advanced or MBC received gemcitabine 1250mg/m$^2$ IV on days 1 and 8 plus doxorubicin 60mg/m$^2$ IV on day 1 every 21 days for a maximum of 6 cycles.

Results: Thirty-five patients were included, and all are evaluable for safety and efficacy. Median age was 47 years (range, 33 to 60 years). Fourteen patients (40%) were post-and 21 (60%) were premenopausal. Prior treatment included mastectomy (23pts); adjuvant non-anthracycline containing combination chemotherapy (18pts); adjuvant hormonal therapy (3pts) and 2 pts did not receive any adjuvant therapy. Twelve patients had metastatic disease at presentation. Seventeen pts were chemo naive. Hormonal receptors were positive in 6, negative in 21, and unknown in 8 pts. Site of metastasis included one site in 15 pts, two sites in 14, and three sites in 6 pts. Complete remission was observed in 6/35 (17.1%) and partial remission in 14/35 (40%) pts, for an overall response rate of 57.1%. Stable disease was observed in 8 (22.9%) and progressive disease in 7 (20%) pts. The median time to tumor progression was 7 months (range, 5-23 months; 95% CI, 6-8 months) and the median survival time was 16 months (range, 6-43 months; 95% CI, 13-19 months). The overall survival at 1 and 2 years was 74.2% and 34.2%; respectively; with 4/35 (11.4%) patients alive at 40 months. A total of 186 cycles of treatment were administered (range2-6 cycles, median 6 cycles). The doses of both doxorubicin and gemcitabine were modified after interim analysis of toxicity following the first 22 cycles administered to the first 10 patients [Mucositis grade 3-4 occurred in 6/10 (60%), grade 3-4 neutropenia in 3/10 (30%), and febrile neutropenia grade 3 in 2/10 (20%) patients] to doxorubicin 50mg/m$^2$ on day 1 and gemcitabine to 1000 mg/m$^2$ on days 1 and 8 in the remaining cycles. After doses reduction, the toxicity was generally tolerable.

Conclusion: The combination of gemcitabine plus doxorubicin after doses modification can be safely administered every 21 days with promising response as first-line therapy for MBC. The response rate, time to disease progression and overall survival rates of this regimen are comparable to other standard therapies for MBC, as well as other gemcitabine combinations.

Key Words: Gemcitabine – Doxorubicin – Metastatic breast cancer.

INTRODUCTION

Approximately 20-85% of patients, with early breast cancer will later develop recurrent and/or metastatic disease, depending on the initial stage, tumor biology, and treatment strategy used. Despite more than 3 decades of research, metastatic breast cancer (MBC) remains essentially incurable and, after documentation of metastasis, the median survival time is approximately 2 years [1].

For women with hormonal-independent disease, chemotherapy is currently the only therapeutic option. Many cytotoxic agents have been available for more than 4 decades for the management of MBC. The most active drugs are the anthracyclines and the taxanes, followed by alkylating agents and antimetabolites and vinca alkaloids. Used as single agents, they produce objective response rate (RR) of 20-60% [2-5]. However, the rare complete responses are short lived, and disease progression is almost inevitable. Combination regimens produce higher
response rate but with no significant improvement in survival [6,7].

Gemcitabine (2', 2'-fluorodeoxycytidine; dFdC) is a cytotoxic nucleoside analog, which differs from other fluoropyrimidines by the fluorine substitution on the ribose ring [8]. The parent compound is sequentially phosphorylated by deoxycytidine kinase to the gemcitabine triphosphate dFdCTP, which is incorporated into DNA, causing masked chain termination. In addition, the diphosphate dFdCDP functions to diminish intracellular deoxynucleoside pools through the inhibition of ribonucleotide reductase [9]. Gemcitabine has in vitro activity against a broad array of human tumor cell lines and has provided objective responses in a variety of human solid tumors including breast cancer [10,11].

The drug’s mild toxicity profile, activity in solid tumors, and relative non–cross-resistance with other classes of drugs offer opportunity for study. The aim of the current study is to evaluate the efficacy and toxicity of gemcitabine in combination with doxorubicin as first line treatment in advanced or metastatic breast cancer patients.

**PATIENTS AND METHODS**

This single institution phase II trial of gemcitabine and doxorubicin administered to patients with locally advanced or MBC was conducted at the Medical Oncology department, National Cancer Institute, Cairo University.

*Patients eligibility:* To be eligible for the study, patients had to be female and aged 18-65 years and have histologically or cytologically confirmed breast cancer with unresectable locally advanced and/or metastatic disease. Patients were required to have at least one bidimensionally measurable lesion that had not been irradiated, with a minimal size in at least one diameter of $\geq 2\text{cm}$ for liver lesions and $\geq 1\text{cm}$ for lung, skin, and lymph node metastases. All patients had to have performance status (ECOG Scale) $\leq 2$, life expectancy of at least 6 months, normal left ventricular ejection fraction ($\geq 50\%$) as determined by echocardiography, negative pregnancy test, normal hematological, renal, and hepatic function (WBC count $\geq 3.5 \times 10^9/\text{L}$, platelet count $\geq 100 \times 10^9/\text{L}$, hemoglobin level $\geq 10\text{g}/\text{L}$; serum bilirubin $<1.5\text{mg/dL}$, ALT and AST levels $<3$ times normal values; ALT and AST levels $<5$ times normal limits allowed in patients with known liver metastases; plasma creatinine level $<1.5$ times normal value). In addition patients should have compliance, mental state and geographic proximity that allow adequate follow-up and they had to provide written informed consent before any study-specific procedure.

Patients were ineligible if they had previously received chemotherapy regimen for metastatic or locally advanced disease (Previous hormonal therapy either on adjuvant setting or for locally recurrent or metastatic disease is allowed); previously received anthracycline in an adjuvant setting (At least 6 months should be elapsed after end of non-anthracycline containing adjuvant regimen before entry on the study); concomitant or previous radiation therapy within 4 weeks before treatment start; pregnancy; evidence of CNS metastases; active infection unless adequately treated; serious concomitant systemic disorders incompatible with the study design; or second primary malignancies (except adequately treated basal cell carcinoma of skin and carcinoma in-situ of uterine cervix). The study was conducted according to the local ethics committee rules.

*Treatment plan:* Gemcitabine was given at a dose of 1250mg/m$^2$ i.v. infusion over 30 minutes on days 1and8 plus doxorubicin 60mg/m$^2$ i.v. on day 1. Cycles were repeated every 21 days.

No new cycles of doxorubicin and gemcitabine were started unless the total leukocyte count was $\geq 3\times 10^9/\text{L}$ and the platelet count $\geq 100\times 10^9/\text{L}$. A full dose of gemcitabine was given on day 8 if the total white blood count and platelet counts were $\geq 2$ and $\geq 50\times 10^9/\text{L}$; respectively. The dose was omitted if these counts were less than 1.99 and 49 $\times 10^9/\text{L}$; respectively or if there was any evidence of bleeding complications.

For non-hematological toxicities other than alopecia, the drugs were given at 50% of planned doses or omitted if common toxicity criteria grade 3 or 4 toxicities occurred. Patients with objective (complete or partial) response or stable disease continued on treatment until disease progression or for a maximum of 6 cycles.
Patients with documented progressive disease were withdrawn from the study.

The primary end point of this study is to assess the efficacy of this regimen: Overall response rates (ORR), time to disease progression (TTP), and overall survival (OS), while the secondary end point is to assess the safety and toxicity profile of this combination.

Study assessment:

Pretreatment assessment included medical history and physical examination, ECG, echocardiography, chest X-ray, computed tomography of abdomen, pelvis and/or chest, and bone scan was conducted within 2 weeks before treatment start. Further assessment conducted within 7 days before treatment start included vital signs, performance status (ECOG), and laboratory tests (hematology and blood chemistry).

Interim analysis assessment of response was done every 2 cycles, at the end of treatment and every 2 months thereafter till evidence of disease progression with the appropriate tests for all patients, clinically and radiologically. In responding patients, the response had to be confirmed a minimum of 4 weeks after the first response had been recorded.

A complete response (CR) was defined as complete disappearance of all known disease determined by two observations not less than 4 weeks apart. A partial response (PR) was 50% or greater reduction of the product of the perpendicular diameters of all measurable lesions. Stable disease (SD) defined as less than 50% reduction or less than 25% increase in tumor size. Progressive disease (PD) was an increase of more than 25% in the product of the perpendicular diameters of all measurable lesions or the appearance of new lesions.

Time to disease progression (TTP) was defined as the time elapsed from the start of treatment to reviewed progression, and survival from initiation of chemotherapy until date of death.

Adverse events were recorded throughout the study and for 28 days after the last administration of study drug. Adverse events were graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC).

Statistical analysis:

The Mann-Whitney statistical test was used to compare results amongst the various patient subgroups. Kaplan-Meier method was used for estimating the probability of survival and time to disease progression [12]. Categorical data were presented in contingency tables with frequencies and percentages, with confidence intervals calculated at the 95% level.

RESULTS

A- Patients characteristics:

From December 1999 to May 2000, 35 patients with MBC were included in this study. The study population was followed-up till February, 2004. All patients were assessable for response and toxicity. The median age was 47 years (range, 33-60); 14/35 (40%) patients were post-and 21/35 (60%) were premenopausal. Invasive duct carcinoma was the predominant pathological type occurred in 34 (97%) patients while lobular carcinoma was encountered in 1/35 (3%) of patients. Hormonal receptors were positive in 6/35, negative in 21/35, and unknown in 8/35 patients. Twenty three patients presented with metastasis after primary surgical treatment; 18 patients had received previous non-anthracline adjuvant chemotherapy (CMF), 3 patients had received prior endocrine therapy in adjuvant setting, and 2 patients did not receive any adjuvant therapy. Twelve patients had metastatic disease at presentation. Seventeen patients were chemo-naive. Ten patients had received hormonal therapy for metastatic disease. The number of tumor sites was only one in 15 patients (43%), two in 14 (40%), and three sites in 6 patients (17%). Lung was the most common site of metastasis in 16/35 patients, liver in 11/35, bone in 8/35, and loco-regional in 16/35 patients. These data are summarized in Table I.

Following the occurrence of extensive mucositis and febrile neutropenia which occurred in initial 10 cases, the dose was subsequently reduced to gemcitabine 1000mg/mg/m² and doxorubicin 50mg/m² in subsequent cycles. Further temporary dose reductions or omissions were done if there is toxicity according to the protocol.

B- Response rate:

Complete remission was observed in 6/35 (17.1%) and partial remission in 12/35 (40%) patients, for an overall response rate of 57.1%. Stable disease was observed in 8 (22.9%) and progressive disease in 7 (20%) patients (Table
Patients with lung metastases and loco-regional recurrences showed better responses than those with hepatic metastases (ORR 56% Vs. 38%; respectively).

**C- Time to tumor progression (TTP) and overall survival (OS):**

All patients with initial response to therapy and those with stable disease (28/35 patients) progressed with a median time to tumor progression of 7 months (range, 5-23 months; 95% CI, 6-8 months, Fig. 1). The median overall survival rate of the whole group was 16 months (range, 6-43 months; 95% CI, 13-19 months). The overall survival at 1 and 2 years was 74.2% and 34.2%; respectively, with 4/35 (11.4%) patients alive at 40 months (Fig. 2).

**Toxicity:**

A total of 186 cycles of treatment were administered (range 2-6 cycles, median 6 cycles). The doses of both doxorubicin and gemcitabine were modified after interim analysis of toxicity following the first 22 cycles administered to the first 10 patients (Mucositis grade 3-4 occurred in 6/10 (60%), grade 3-4 neutropenia in 3/10 (30%), and febrile neutropenia grade 3 in 2/10 patients (20%)) to doxorubicin 50mg/m² on day 1 and gemcitabine to 1000mg/m² on days 1 and 8 in the remaining cycles. After doses reduction, the toxicity was generally tolerable. The delivered dose intensity for doxorubicin and gemcitabine was 16.6mg/week and 666mg/week, respectively. The most significant grade 3 and 4 adverse events were mucositis and hematological toxicities. Anemia was encountered in 23/35 (65%) of patients and was mainly of grade 1. Leucopenia grade III and IV occurred in 5/35 (14.2%) patients. Four episodes of febrile neutropenia were developed, necessitated hospital admission for hemodynamic instability in two cases but no treatment-related mortality has been reported. Thrombocytopenia was seen in nearly 50% of patients mainly grade I and II. Mucositis was recorded in 27 patients, reaching GIII in 6/35 (17.1%) and G IV in 2/35 (5.7%) patients. Other non-hematological toxicities included alopecia grade III in 25/35 (71%) and vomiting grade I in 27/35 (77.1%) patients. Grade I elevation in hepatic transaminases occurred in 11/35 patients (31%) but no increase in serum bilirubin. No cardiac toxicity was encountered. These data are summarized in Table (3).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Number (%)</th>
</tr>
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<tbody>
<tr>
<td>Overall Response</td>
<td>20/35 (57.1)</td>
</tr>
<tr>
<td>Complete Response</td>
<td>6/35 (17.1)</td>
</tr>
<tr>
<td>Partial Response</td>
<td>14/35 (40)</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>8/35 (22)</td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>7/35 (20)</td>
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<tr>
<td>Median TTP (months)</td>
<td>7m (range, 5-23m; 95% CI, 6-8m)</td>
</tr>
<tr>
<td>Median overall survival (months)</td>
<td>16m(range, 6-43m; 95% CI, 13-19m)</td>
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</table>

CI: Confidence interval
DISCUSSION

Metastatic breast cancer is still an incurable disease and a major goal of therapy is palliation of symptoms. Single chemotherapeutic agents produce response rates ranging from 25% as with platinum compounds to about 60% as with anthracyclines or taxanes. It may also be useful to combine drugs with different resistance patterns, and non overlapping toxicities. Anthracyclines based combinations had been shown to be pivotal in treatment of MBC. The combinations of anthracyclines and taxanes produced the highest response rates but overlapping hematological, cardiac toxicities as well as mucositis are of concern especially when the main aim is palliation [6,7].

On the other hand, gemcitabine demonstrates antitumor activity by targeting specific phases of the cell cycle, primarily DNA synthesis (S phase) and the boundary between the G1 and S phases [8,9]. 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 [13-17]. Gemcitabine has no apparent multidrug resistance, has a mild hematological toxicity profile and is generally well tolerated by patients, [18,19]. Thus, gemcitabine and doxorubicin is a logic combination for treatment of this disease.

Thirty five patients were included in the current study. None of these patients received prior chemotherapy for metastatic disease and they are all anthracycline naïve. An overall response rate of 57.1% was obtained including 17.1% CR with a median time to disease progression of 7 months and median overall survival of 16 months. Using doxorubicin dose of 60mg/m² and gemcitabine doses of 1250mg/m² in the first 10 patients was associated with higher toxicity profile with hospitalization of some patients due to febrile neutropenia mainly and delay in treatment of other patients due to extensive mucositis.

After using modified doses, toxicities were tolerable, with no patients requiring hospitalizations, or blood product support. No treatment related mortality was associated with either dose. There was no change in response rate, TTP or survival when doses were reduced by 25% in subsequent 25 patients after initial patients had GIII, IV mucositis and febrile neutropenia.

These results compare favorably with other standard combinations [5]. Furthermore, gemcitabine based-combinations including taxanes, navelbine, cisplatin, produced similar results (ORR 69, 60, 45, 39%; respectively) with a higher cost and/or toxicity [20-23].

On the other hand, Perez-Manga et al. [24] reported an ORR of 55% with CR rate of 7% and a median survival of 27 months using a similar combination yet with slightly higher dose intensity (doxorubicin 18.7mg/w and gemcitabine 750mg/w compared with 16.6mg/w and 666mg/w; respectively) than that used in our study. Furthermore, they used the combination with a different schedule through giving each of the drugs on weekly basis (D1, D8, and D15). In their study which included 42 patients, one treatment related mortality occurred and it was considered acceptable. Their study, which was the first study published about this combination, showed that gemcitabine and doxorubicin did not significantly affect the pharmacokinetics of either drugs.

In conclusion, the combination of gemcitabine and doxorubicin after dose modification give encouraging results in patients with metastatic breast cancer with generally tolerable and manageable toxicity. Survival results compared favorably with other combinations. Yet the best dose and schedule needs to be defined. The efficacy and tolerability of combination needs to be tested in larger randomized trials with formal measurement of quality of life.

REFERENCES


