Phase II study of gemcitabine plus epirubicin plus paclitaxel in metastatic breast cancer patients

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ABSTRACT
Although metastatic breast cancer is essentially incurable, patients achieving a complete response may be good candidates for long term survival. Gemcitabine, epirubicin and paclitaxel have different mechanisms of action. Therefore, we conducted this phase II study to assess efficacy and safety of gemcitabine plus epirubicin plus paclitaxel (GET) combination therapy in metastatic breast cancer. The study enrolled 21 women with pathologically confirmed and measurable metastatic breast cancer who were not previously treated with gemcitabine and paclitaxel and prior doxorubicin cumulative dosage was no more than 240 mg/m² and epirubicin cumulative dosage 360 mg/m². Median ECOG performance status was 0. Fifteen patients (71.4%) had visceral metastases and most of them had liver and lung involvement as the predominant site. Treatment schedule was as follows: gemcitabine 1000 mg/m² was administered intravenously in 30 minutes on days 1 and 4 and epirubicin 90 mg/m² was administered intravenously 30 minutes on day 1 following gemcitabine administration and paclitaxel 175 mg/m² was administered intravenously in 3 hours on day 1 starting immediately after epirubicin. Objective response rate was 57.1% with 14.2% CR, and 42.8% PR. Median time to progression and overall survivals were 11 and 19 months respectively. Treatment of five patients was discontinued due to toxicity. Grade 3-4 neutropenia, anemia and thrombocytopenia were observed in 100%, 52.3%, and 42.8% of patients respectively. First and second dose reductions due to myelotoxicity were performed in 66.6% and 42.8% of patients respectively. Only 33.3% of patients received scheduled dose. In our study, the GET regimen has comparable efficacy to anthracycline-alkylator or anthracycline-taxane combination but requires proportionally high dose modifications due to myelotoxicity. [Turk J Cancer 2005;35(4):159-165].

KEY WORDS:
Gemcitabine, epirubicin, paclitaxel, metastatic breast cancer

INTRODUCTION
Despite all available treatment options, metastatic breast cancer (MBC) is essentially incurable and the median survival time is 12 to 24 months after documentation of metastasis (1). Although primary goals of treatment are prolongation of time to progression, disease free survival and overall survival, the chemotherapy is generally palliative in metastatic breast cancer. Nevertheless, the patients who achieve a complete remission after chemotherapy may remain in this state for prolonged period (2,3).

Anthracyclines have been considered as one of the most active agents in the metastatic breast cancer and regimens containing anthracyclines provide 50% to 80% objective response and 15-20% clinical complete response rate in metastatic breast cancer (2-4). Paclitaxel plus epirubicin combination is effective with response rates of 50-70% and safe (5). The combination of paclitaxel and gemcitabine (GT) is challenging because of the different mechanisms of action and generally non-overlapping toxicity profiles. Phase I studies indicated that GT combination is well tolerated and can be administered with both drugs at full doses (6). GT doublet was evaluated in phase II and III
trials where the objective response rates were reported as
45.4-69.0% with 15.9-26% CR (7-11). Heavily pretreated
and chemonaive patients were evaluated in this trial and
GT combination was found to be efficient in both groups.
The mechanism of action and main adverse effects of
gemcitabine and anthracyclines do not overlap. Limited
number of studies shows that gemcitabine and anthracycline
doublet was found to be feasible and well tolerated (12-14).

Anthracycline and taxanes belong to most active agents
used in breast cancer treatment. Single-agent gemcitabine
is moderately active and well tolerated (14). Gemcitabine,
epirubicin and paclitaxel have different mechanism of
action, thus GET is an attractive regimen for metastatic
breast cancer.

Therefore, we conducted this phase II study to assess
the efficacy and safety of gemcitabine plus epirubicin plus
paclitaxel (GET) triplet combination therapy in metastatic
breast cancer.

**PATIENTS AND METHODS**

Histologically confirmed metastatic breast cancer patients
with at least one bidimensionally measurable disease were
eligible for study enrollment. Patients had to meet the
following additional eligibility criteria: age 18-70 years,
life expectancy >3 months, Eastern Cooperative Oncology
Group (ECOG) performance status 0-2, normal left ven-
tricular ejection fraction by echocardiography, adequate
marrow, renal and hepatic function (absolute neutrophil
count ≥ 2000/µL, platelet count ≥ 100,000/µL, and total
bilirubin and serum creatinine ≤ 1.25 x upper normal limit
(UNL). Prior chemotherapy for metastatic disease or adju-
vant/neoadjuvant treatment were stopped at least 6 months
non-anthracycline containing regimens and anthracycline
containing regimens for at least 12 months. A prior doxo-
rubicin cumulative dosage was no more than 240 mg/m²
and epirubicin cumulative dosage 360 mg/m². Patients who
could not have been treated with taxane and gemcitabine
were eligible for the study. Concurrent hormonal therapy
during the study was not allowed.

Before initiation of therapy, all patients underwent
staging work-up which included a complete history and
physical examination, a complete blood cell count with
differential, chemistry profile, ECG, echocardiography,
and tumor measurement with appropriate radiographic or
computed tomography scan for disease assessment.
Complete blood cell counts with differential were performed
on day 1 and 4 and subsequently weekly. Cardiac toxicity
was evaluated by echocardiography. Chemistry profile
(urea, creatinine, electrolytes, and liver function tests) and
toxicity assessment were performed every 3 weeks. Lesions
were evaluated for response at every two cycles with
repeated measures performed as the original means of
assessment. However, the evaluation was repeated in case
of any disease related symptoms or signs.

Exclusion criteria included bone metastases as the only
site of disease, previous radiation therapy on target lesion,
symptomatic brain metastases, significant cardiac disease,
a past or concurrent history of other neoplasm (except
nonmelanoma skin cancer or cervical carcinoma in situ),
previously irradiation to a field encompassing more than
%30 of bone marrow, pregnancy, breast feeding. Patients
with other serious medical conditions potentially comprom-
ising study participation were also excluded. All patients
were required to provide written informed consent.

Treatment regimen consisted of gemcitabine 1000
mg/m², epirubicin 90 mg/m² and paclitaxel 175 mg/m².
Gemcitabine was administered intravenously in 30 minutes
on days 1 and 4. Epirubicin was administered intravenously
in 30 minutes on day 1 following gemcitabine administra-
tion. Paclitaxel was administered intravenously in 3 hours
on day 1 starting immediately after epirubicin. Each pacli-
taxel administration included premedication with dexam-
ethasone 20 mg p.o. 12 and 6 hours before therapy; diphen-
hydramine 50 mg, and ranitidine 50 mg i.v. 30 minutes
before paclitaxel. Treatment regimen was given at every
21 days for a maximum of six cycles.

Dose modifications were based on weekly monitoring
of complete blood count and assessment of other toxicities.
If absolute neutrophil count were less than 1500/µL, and/or
the platelet count less than 100000/µL on day 21, the
treatment was delayed by weekly intervals. If hematologic
recovery was not achieved after six weeks, the treatment
was discontinued. Prophylactic hematopoietic growth
factors were not administered routinely. The chemotherapy doses were reduced at 20% if there was febrile neutropenia, documented infection, severe bleeding, grade 3-4 thrombocytopenia, grade 4 neutropenia, or ≥grade 3 non-hematologic toxicity (except alopecia, vomiting, musculoskeletal pain). If same toxicities were repeated, second dose modification was made. Only epirubicin dose was reduced to 20% in the second dose modification. Treatment was discontinued in case of progressive disease or unacceptable toxicity.

Toxicity was evaluated according to the National Cancer Institute Common Toxicity Criteria. Tumor response was graded according to the WHO criteria. Complete response (CR) was defined as the disappearance of all clinical evidence of tumor, and the absence of any disease-related symptoms for a minimum four weeks. Partial response (PR) was defined as a ≥50% reduction in the sum of the products of the perpendicular diameters of all measurable lesions, without the appearance of any new lesions for at least four weeks. Stable disease (SD) was defined as a less than 50% decrease or a less than 25% increase in tumor size for at least four weeks. Progressive disease (PD) was defined as a ≥25% increase in the sum of the products of the perpendicular diameters of any measurable lesions or in the estimated size of an immeasurable lesion or any new lesion. In the case of bone metastases, CR was defined as a disappearance of all lesions on X-ray or scan for at least four week, PR was defined as partial decrease in size of lytic lesions, recalcification of lytic lesions or decreased density of blastic lesions for at least 4 weeks. After the last course of chemotherapy, patients were followed every 3 months until death to monitor progression and survival.

Statistical method

Patients, who received at least two cycles of therapy, were considered assessable for response. Patients who received at least one course of therapy were assessable for toxicity. Time to progression was considered from the beginning of therapy to the date of disease progression. Overall survival was measured from the date of the first course of therapy to the date of death or last follow-up examination. Survival curves were plotted according to the Kaplan Meier method and confidence intervals for response rates were calculated using methods for exact binominal confidence intervals (15,16).

RESULTS

A total of 21 patients were enrolled in the study. Pretreatment characteristics of patients are listed in table 1. All patients were considered eligible for response and toxicity evaluations. Mean age was 50.2 years (range: 38-68 years). Median ECOG performance status was 0. Fifteen patients (71.4%) had visceral metastases and most of them had liver and lung involvement as the predominant site. Fifteen patients had previously received adjuvant or neo-adjuvant anthracycline based chemotherapy and 9 patients had previously received hormonotherapy. A total of 21 patients received 105 courses of chemotherapy, with a median of 6 courses per patients (range: 2-6 courses).

In twenty one evaluable patients, the objective response rate was 57.1% (12 patients; 95% CI: 35.9% - 78.2%) with 14.2 (3 patients; 95% CI: 0% - 29.1%) CR, and 42.8% (9 patients; 95% CI: 21.6% - 63.9%) PR. Additionally, stable and progressive disease was observed in 28.5% (6 patients) and 14.2% (3 patients) respectively (Table 2). The median time to progression (TTP) was 11 months (range: 2- 28 months; 95% CI: 7% - 15%) (Figure 1) and the median overall survival (OS) was 19 months (range: 4-45+ months; 95% CI 16% - 22%) (Figure 2). One and two year survival rates were 71.4% and 9.5%, respectively.

All patients were assessable for toxicity. Toxicity data is listed in table 3. Hematologic toxicities were the major dose-limiting toxicities. Treatment of five patients was discontinued due to toxicity. Grade 3-4 neutropenia, anemia and thrombocytopenia was observed in 21 (100%), 11 (52.3%), and 9 (42.8) patients respectively. First and second dose reductions due to myelotoxicity were performed in 14 (66.6%) and 9 (42.8%) patients, respectively. Seven (33.3) patients received scheduled dose. Major hematologic toxicities were observed in 20 patients after the first two cycles. In addition, 7 (33.3%) patients developed febrile neutropenia. Twelve patients required G-CSF support. Grade 3 or 4 bleeding, cardiotoxicity, hepatotoxicity were not observed. Toxicity related death was not observed.
Table 1  
Pretreatment characteristics of patients and tumors (N=21)  

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<tr>
<th>Characteristics</th>
<th>Mean age(years)</th>
<th>Range</th>
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<th>%</th>
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<td>6</td>
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<tr>
<td>4</td>
<td>2</td>
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<td>9.5</td>
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<tr>
<td>Liver</td>
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<td>Bone</td>
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<td>Adjuvant or neoadjuvant FEC</td>
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<tr>
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<tr>
<td>No prior chemotherapy</td>
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<td>28.5</td>
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<tr>
<td>Prior hormonotherapy</td>
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<tr>
<td>Adjuvant therapy only</td>
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<td>33.3</td>
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<tr>
<td>Metastatic therapy only</td>
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<td>4.7</td>
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<tr>
<td>Both adjuvant and metastatic therapy</td>
<td>1</td>
<td></td>
<td>4.7</td>
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</table>

*Surrenal gland and pleura

FEC: fluorouracil 500mg/m², epirubicin 50 mg/m², cyclophosphamide 500 mg/m²; CMF: fluorouracil 600mg/m², methotrexate 40 mg/m², Cyclophosphamide 500 mg/m²

Table 2  
Response rates  

<table>
<thead>
<tr>
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<th>N patients</th>
<th>%</th>
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<tr>
<td>Objective Response</td>
<td>12</td>
<td>57.1</td>
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<tr>
<td>Complete response</td>
<td>3</td>
<td>14.2</td>
</tr>
<tr>
<td>Partial response</td>
<td>9</td>
<td>42.8</td>
</tr>
<tr>
<td>Stable disease</td>
<td>6</td>
<td>28.5</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>3</td>
<td>14.2</td>
</tr>
</tbody>
</table>

Fig 1. Kaplan-Meier analysis of time to progression. Median TTP=11 months

Fig 2. Kaplan-Meier analysis of overall survival. Median overall survival=19 months
DISCUSSION

In our phase II study, we evaluated the efficacy and tolerability of 3-weekly paclitaxel 175 mg/m² (3-hour infusion) and gemcitabine 1000 mg/m² on day 1 and 4 and epirubicin 90 mg/m² at every 21 days regimen in metastatic breast cancer. The overall response rate was 57.1% with a 14.2% CR, and 42.8% PR. Time to progression and overall survivals were 11 and 19 months respectively. Early phase II trials which evaluate anthracycline paclitaxel combination in metastatic breast cancer, have shown that this combination is very active, with overall response rates ranging 75-95% and with CR rates as high as 40% (17-19). Phase III trials that compared anthracycline-paclitaxel combinations with standard anthracycline-alkylator regimens were not to support these results (20-24). Only one trial demonstrated a survival advantage for the paclitaxel containing regimens (24). However, the CR rates in all this phase III trials were lower than expected. The response rate and overall survival of our phase II study were similar to paclitaxel and anthracycline containing phase III trial results.

The authors who take high CR as a goal conducted GET tripled chemotherapy trials (25,26). The first phase II monocenter trial showed that the response rate was 92% with 31% CR (27). After the impressive results, multicenter phase II trial was conducted. In this trial overall response rate was 71% with 15% CR (27). In a recently declared phase III study comparing gemcitabine plus epirubicin plus paclitaxel and fluorouracil plus epirubicin plus cyclophosphamide, Zielinski et al. (28) found the response rates as 62.3% and 51.2% respectively with an insignificant difference. In phase II and III, GET trial grade III-IV neutropenia, thrombocytopenia, anemia and febrile neutropenia were observed in 62-93%, 4-28%, 2-21% and 6-12% respectively. Neutropenia, leukopenia, febrile neutropenia, thrombocytopenia, anemia, allergy polyneuropathy, and mucositis were significantly higher in GET arm in phase III trial reported by Zielinski et al. Other toxicities were similar in two arms. In our study, major dose limiting toxicities were hematologic toxicities which neutropenia (100%), thrombocytopenia (42.8%), and febrile neutropenia were observed in 15-28%, 5-5.4% and 2.3-6.8% of the patients, respectively (7-11).

<table>
<thead>
<tr>
<th>Table 3</th>
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<tbody>
<tr>
<td>Toxicities (105 cycles)</td>
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<tr>
<td></td>
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<tr>
<td>Neutropenia</td>
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<tr>
<td>Anemia</td>
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<tr>
<td>Thrombocytopenia</td>
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<tr>
<td>Infection</td>
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<tr>
<td>Nausea/vomiting</td>
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<tr>
<td>Diarrhea</td>
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<td>Mucositis</td>
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<td>Neurotoxicity</td>
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<td>Cardiac</td>
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</table>
The toxicity of our previous gemcitabine (1000 mg/m² d1,8) and paclitaxel (175 mg/m² d1) studies were lower than this study. Grade 3 or 4 toxicity was observed in 34.6% of patients and 76.9% of the patients completed the full treatment course (in press; Cancer Investigation).

Although GET combination was not superior to standard anthracycline-alkylator regimen, these agents are already under consideration by the NSABP for inclusion in an adjuvant trial, where GT would follow the anthracycline-alkylator regimen (personal communication).

In conclusion, our small numbered study shows that the GET regimen was effective but requires high proportional dose modification due to myelotoxicity.

References


