

Gemcitabine and Cisplatin Combination Chemotherapy as a First-Line Treatment in Patients with Metastatic Breast Cancer

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ABSTRACT

Purpose: The objectives of this phase II prospective study were to evaluate the efficacy and toxicity of Gemcitabine plus cisplatin as a first line chemotherapy in female patients with metastatic breast cancer who previously received anthracyclin-based regimen as adjuvant chemotherapy.

Patients and Methods: Twenty five patients with metastatic and at least one bi-dimensionally measurable lesion were included in this study. Adequate bone marrow reserve, adequate hepatic and renal functions and performance status ≤ 2 were required. Patients have previously received anthracyclin based-chemotherapy as adjuvant. Treatment consisted of Gemcitabine 1250 mg/m² on days 1 and 8 and cisplatin 75 mg/m² on day 1, cycles were repeated at 3-week intervals.

Results: 25 patients were evaluable for toxicity and 22 patients for response. Overall response was 54.5%. Complete response was reported in 13.6% of patients and partial response was reported in 40.9% of patients. Six patients (27.2%) had stable disease and disease progression was reported in (18.2%) of patients. Response was reported in all metastatic sites. Toxicities included grade 3,4 vomiting in 32% and grade 3, 4 neutropenia in 12%, grade 3, 4 thrombocytopenia in 32%. Only one case of neutropenic fever was reported. Renal and neurotoxicity was encountered in 12% and alopecia grade 1, 2 in 8% of patients. No treatment related death was reported. The median overall survival was 14.8 months (range: 2 to 18.5).

Conclusion: Gemcitabine and cisplatin combination chemotherapy is active and well tolerated regimen for patients with metastatic breast cancer. This regimen represents a therapeutic option for patients receiving front line therapy for their metastatic breast cancer. Phase III randomized trial is needed for comparison with other 2nd line regimens to define the exact role of this combination.

Key Words: Gemcitabine - Chemotherapy - Breast cancer.

INTRODUCTION

Gemcitabine is a nucleoside analogue that demonstrates anti-tumor activity by targeting

specific phases of the cell cycle, primarily DNA synthesis (S phase) and the boundary between G1 and S phases [1-3]. 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 [4-6]. Based on its single agent activity, modest toxicity and novel mechanism of action, combination therapy with cisplatin may provide clinical benefit in patients with metastatic breast cancer.

The development of new, clinically effective combination chemotherapy regimens with improved efficacy, more convenient dosing schedules, better tolerability and fewer side effects may increase survival and improve quality of life for many patients with advanced and metastatic breast cancer [4].

There is now considerable evidence on the role of cisplatin either single agent or in combination chemotherapy in previously untreated advanced breast cancer patients [7]. Recently, promising results have been obtained with cisplatin-containing schemes as second-line treatment [8].

However, most published studies are uncontrolled and often involve small patient samples. There were five randomized trials compared cisplatin combination chemotherapy with conventional regimens. These trials showed that first line combination chemotherapy with cisplatin may achieve higher response rates than conventional schedules, without significant benefits in response duration. Because of the relatively few cases included in each study, the

findings on time to progression and overall survival were inadequate [4,5,6,9].

This study was conducted to determine clinical efficacy and safety of Gemcitabine and cisplatin combination in patients with metastatic breast cancer.

PATIENTS AND METHODS

This is a phase II single arm study including 25 patients with metastatic breast cancer presented to oncology department Assiut University between Nov (2001) to Nov (2002).

Eligibility criteria:

- 1- Patients with histologically confirmed metastatic breast cancer, bidimensionally measurable disease.
- 2- No prior chemotherapy for metastatic disease and no history of concomitant malignancy.
- 3- Patients were required to have an Eastern Cooperative Oncology Group performance status ≤ 2 .
- 4- Adequate bone marrow reserve (hemoglobin ≥ 10 g/dL, absolute granulocyte count ≥ 1.500 and a platelets count $\geq 100.000/UL$).
- 5- Adequate renal functions (serum creatinine concentration ≤ 1.25 X upper normal limit or creatinine clearance more than 60 mL/min), liver functions (serum bilirubin level ≤ 1.25 X upper normal limit).
- 6- Previous adjuvant or neoadjuvant chemotherapy (Anthracyclin-based regimen) or hormonal treatment.
- 7- Life expectancy ≥ 3 months.

Treatment plan:

Before study entry, patients underwent a complete medical history and physical examination, including evaluation of performance status, body surface area and vital signs. Radiologic assessments were performed to determine the extent of disease (e.g. chest X-ray, abdominal sonar, computed tomography, MRI and isotopic studies). Laboratory studies including: complete blood picture, kidney and liver functions and tumor markers (CA15-3) were also performed.

Treatment schedules:

Eligible patients were treated with the following:

Gemcitabine 1250 mg/m², intravenous infusion over 30 minutes on day 1 and 8 plus cispl-

atin 75 mg/m², intravenous infusion over 1 hour on day 1. Cisplatin treatment was administered with pre-hydration and post-hydration measures. Chemotherapy was repeated every 21 days. Chemotherapy was administered for a maximum of eight cycles and was discontinued in case of unacceptable toxicity, treatment delay longer than 2 weeks, disease progression or patient refusal.

Evaluation:

Patients were evaluated regularly every three weeks with physical examination, complete blood picture, laboratory studies and toxicity assessments were performed. Appropriate radiological assessments were performed after 2 cycles. After a response was documented repeated study was performed after two additional cycles. If the patient continued in response status these studies were repeated again after 3 cycles unless the clinical situation required an earlier evaluation.

In term of response criteria, the size of measurable lesions were determined before each course of therapy and reported as the product of the longest diameter and its perpendicular. Responses were categorized as follows: complete response (CR), complete disappearance of all measurable and assessable disease lasting at least 4 weeks, partial response (PR), $\geq 50\%$ decrease in the sum of the products of the bidimensional perpendicular diameters of all measurable lesions lasting at least 4 weeks, no progression of assessable disease, no new lesions, no disease related symptoms, stable disease (SD), did not qualify for CR, PR or progressive disease. Progressive diseases (PD), $\geq 25\%$ increase, appearance of any new lesion that had disappeared, appearance of any new lesion site, clear worsening of any assessable disease, or failure to return for evaluation because of death or deteriorating conditions related to disease progression. Toxicity was graded using the National Cancer Institute common toxicity criteria [10].

Statistical analysis:

Duration of response was measured from initiation of treatment for partial response and from time when response was first documented for complete response. Time to progression and survival were calculated from the date of first

chemotherapy cycle to the date of disease progression or the date of death respectively. Duration of response, time to progression and overall survival were assessed using the Kaplan-Meier method [10].

RESULTS

Patient characteristics:

A total of 25 patients were enrolled in the present study. Three patients were not assessable for response, two of them received only one cycle and one patient had developed hepatorenal failure after one cycle. Baseline clinical characteristics of enrolled patients (25 Pts) are listed in Table (1). The median age was 48 years and performance status were 0 in 40%, 1 in 52% and 2 in 8% of patients. Visceral metastases were reported in 80% of patients (48% liver and 32% lung) while bone metastasis and soft tissue disease were reported in 8% and 12% of patients respectively. The majority of patients had only one site of metastasis (72%).

Twenty patients had previously received adjuvant chemotherapy (Anthracycline based). Anthracycline resistance was defined as progression while on adjuvant anthracycline based chemotherapy (progression 4 weeks after the last dose of anthracycline). The median number of cycles was 4 cycles. Hormonal treatment were reported in 11 patients whose hormonal receptors were positive while 20 patients had received adjuvant radiotherapy 12 patients (48%) had relapsed in a period < 1 year while (20%) of patients had relapsed > 3 years after adjuvant therapy.

Responses:

Twenty two patients were assessable for response. The overall objective response rate for these patients was 54.5% (95% confidence interval 38.3%-76.7%) with 3 (CR) 13.6% and 9 PR (40.9%). Six patients (27.2%) had evidence of stable disease and the remaining 4 patients had disease progression (18.2%). The median time to response was 2 months and the median duration of response was 5 months (range 1-16 months) without difference between complete and partial response (Table 2). Response according to disease sites were as follows: soft tissue (66.7%), bone (50%), liver (60%) and lung

(43%). Response rate according to number of metastatic sites was as follows: one site 60% (9 out of 15 patients); two sites 40% (2 out of 5 patients) and three sites, 50% (one of two patients) (Table 3). Response rate in relation to hormonal receptors status, previous adjuvant chemotherapy and disease-free intervals had no statistical significant difference.

The median time to tumor progression was 8 months (95% confidence interval 7.2 to 10.8 months) and median overall survival was 12.8 months (95% confidence interval 10.4 to 15.2 months) Figs. (1 & 2).

Toxicity:

All patients evaluable for toxicity received more than one cycle of chemotherapy. There was no reported toxic related death. Overall toxicities were listed in Table (4). The major hematologic toxicity was observed with grade 3 and 4 thrombocytopenia (28% and 4%) followed by neutropenia in 8% and 4% of patients respectively. Neutropenic complications were rare with only one episode of neutropenic fever. Neausea and vomiting was the major non-hematologic toxicity. Grade 3 and 4 were reported in 28% and 4% of patients. 8% of patients had developed grade 2 alopecia. Peripheral neuropathy was recorded in 3 patients (12%). Fatigue (mild to moderate) was reported as subjective treatment-related toxicity in 40% of patients. One patient had developed hepatorenal failure.

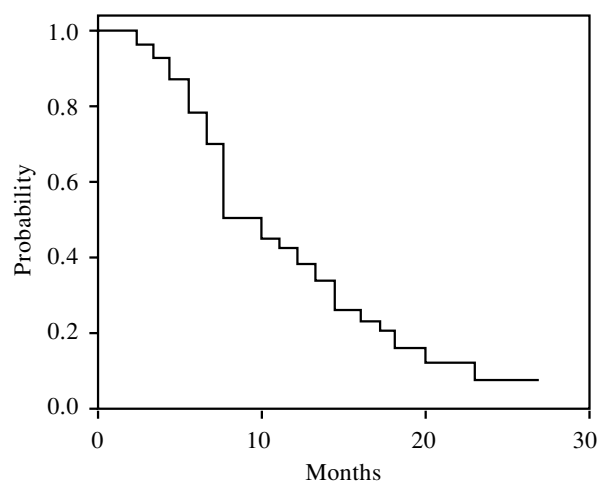


Fig. (1): Time to progression in metastatic breast cancer patients received Gem-Cis as first line treatment.

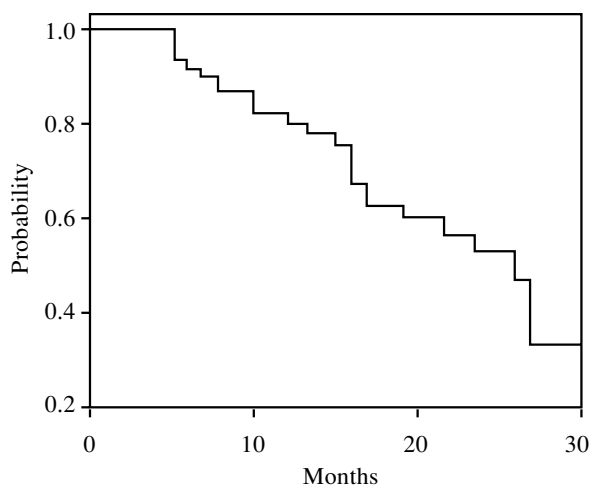


Fig. (2): Overall survival of patients received Gem-Cis as first line treatment.

Table (1): Patients characteristics.

| Characteristic | No. of patients | % |
|----------------------------------|-----------------|----|
| Patients enrolled | 25 | |
| Patients assessable | 22 | |
| <i>Age (years):</i> | | |
| Median | 48 | |
| Range | 32-65 years | |
| <i>Performance status:</i> | | |
| 0 | 10 | 40 |
| 1 | 13 | 52 |
| 2 | 2 | 8 |
| Premenopausal | 18 | 72 |
| Postmenopausal | 7 | 28 |
| <i>Hormonal receptor status:</i> | | |
| Positive | 11 | 44 |
| Negative | 14 | 56 |
| <i>Dominant disease site:</i> | | |
| Soft tissue | 3 | 12 |
| Bone | 2 | 8 |
| <i>Visceral:</i> | | |
| Liver | 12 | 48 |
| Lung | 8 | 32 |
| <i>No. of disease sites:</i> | | |
| 1 | 18 | 72 |
| 2 | 5 | 20 |
| 3 | 2 | 8 |
| <i>Disease-free intervals:</i> | | |
| < 1 year | 12 | 48 |
| 1-3 years | 8 | 32 |
| > 3 years | 5 | 20 |

Table (2): Response for assessable patients (N = 22).

| Response | No. of patients | % |
|------------------------------|----------------------|------|
| Overall response (CR+PR) | 12 | 54.5 |
| CR | 3 | 13.6 |
| PR | 9 | 40.9 |
| Stable disease | 6 | 27.2 |
| Progressive disease | 4 | 18.2 |
| <i>Duration of response:</i> | | |
| Median time | 5 (range 1-16 month) | |

Table (3): Response according to disease site and number of metastatic disease.

| Site | Number | % of response |
|-------------|--------|---------------|
| Soft tissue | 2/3 | 66.7 |
| Bone | 1/2 | 50 |
| Liver | 6/10 | 60 |
| Lung | 3/7 | 43 |
| 1 site | 9/15 | 60 |
| 2 sites | 2/5 | 40 |
| 3 sites | 1/2 | 50 |

Table (4): Hematologic and non-hematologic toxicity in 25 enrolled patients.

| Toxicity | Grade of toxicity | | | | | |
|---------------------|-------------------|----|-----|----|-----|---|
| | 1-2 | | 3 | | 4 | |
| | No. | % | No. | % | No. | % |
| Anemia | 2 | 8 | 2 | 8 | - | - |
| Neutropenia | 10 | 40 | 2 | 8 | 1 | 4 |
| Thrombocytopenia | 7 | 28 | 7 | 28 | 1 | 4 |
| Neutropenic fever | - | - | 1 | 4 | - | - |
| Nausea and vomiting | 10 | 40 | 7 | 28 | 1 | 4 |
| Mucositis | 6 | 24 | - | - | - | - |
| Renal toxicity | 3 | 12 | - | - | 1 | 4 |
| Neurotoxicity | 3 | 12 | - | - | - | - |
| Alopecia | 2 | 8 | - | - | - | - |

DISCUSSION

The management of metastatic breast cancer (MBC) is a major clinical challenge for oncologist. Despite all available systemic therapy, MBC remains essentially incurable with median survival time ranging from 18 to 24 months [11]. The goals of treatment must be kept in mind that MBC is chronic illness, with period of reactivation and remission and a course of multiple therapeutic maneuvers. In this setting, optimal palliation becomes paramount. However, there might be a very small subset of MBC patient who can enjoy very prolonged survival and possibly cure, with aggressive multidisciplinary treatment. This subgroup must be accurately and timely identified so that the appropriate therapeutic approach is initiated [12,13].

The optimal schedule of administration of combination chemotherapy in MBC remains controversial and the decision must be individualized for each patient. Ideally, a combination regimen should meet three criteria: pre-clinical evidence of synergy, no cross-resistance between the components and non-overlapping toxicity profiles [4,14].

Most of the patients relapsed after adjuvant CMF combination had been salvaged by an anthracycline-containing regimen. Today, more patients receive an anthracycline-containing regimen in adjuvant bases. Therefore, there is additional concern about the choice of systemic chemotherapy after relapse especially when considering the potential myocardial toxicity of anthracycline and irradiation of chest wall. For this reason, attempts at designing different drug combinations have been carried out in the past. Recently, new drugs have been found to be effective in metastatic breast cancer. Gemcitabine and cisplatin are active drugs in the treatment of MBC. They possess different mechanisms of action, lack of cross-resistance and have non-overlapping toxicities. They have also demonstrated synergy in pre-clinical (ex vivo human tumor models) and clinical settings. Nagourney et al. [9] had concluded that combination of Gemcitabine and cisplatin is highly active in the ex vivo analysis of human tumor primary cultures and had identified relapsed breast cancer as an attractive target for this combination [9]. A comparison of ex vivo results from previously treated versus previously untreated breast cancer specimens revealed com-

parable degree of sensitivity with a trend toward greater sensitivity and synergy in previously treated group [9,15].

There are two important aspects of the early clinical evaluation of gemecitabin deserve attention and have been reviewed concisely. Most phase II studies identified the recommended dose at 800 mg/m² in 30 minutes infusion weekly for 3 weeks and repeated after 4 weeks. However, less heavily pre-treated patients can tolerate much larger doses and Gemcitabine 1200 mg/m² is now recommended in previously untreated patients, the other important aspect was the observation that Gemcitabine is cleared from the plasma 40% faster in men than in women. This will require a reassessment of toxicity data and consider sex as a variable in evaluation [5].

Based on the previously reported results of phase I and II trials of Gemcitabine and cisplatin in treatment of metastatic breast cancer, this phase II study was conducted to evaluate the activity and tolerability of this regimen. In this study, 80% of patients received prior adjuvant chemotherapy (anthracyclin-based) and adjuvant radiotherapy as well, but non had received prior treatment for metastatic disease. The overall objective response rate was 54.5% (3 CR, 9 PR) in the 22 assessable patients. In addition tumor growth control (overall response + stable disease) was 81.8%, so a greater proportion of patients derived considerable palliative benefit from this combination therapy. Response was observed in all disease sites, being 66.7% in soft tissue, 50% in bone and 58.3%, 62.5% in liver and lung respectively.

It is interesting to mention that there is an ongoing controversy regarding the most relevant end points of MBC trials. Clinical trials in the metastatic setting seldom use overall survival (OS) as the primary end point due to practical limitation particularly related to sample size. Time to progression (TTP) and response rate (RR) are the most commonly used primary end points and serve as a surrogate marker for (OS). However, higher (RR) and longer (TTP) do not always translate into detectable survival advantages. This may partially explained by the fact that the extent to which these surrogate markers end points correlate with (OS), is influenced by the stage of disease, trial design (e.g cross over encouraged or prohibited) and number of

events at the time of analysis [11,7]. The majority of MBC trials published so far are under powered to detect small survival gains, particularly, for second and subsequent lines of chemotherapy [11]. Another explanation is related to the pattern of breast cancer growth, with a typical Gompertzian curve, showing that, when the rate of cancer cell killing reaches a certain point, the rate of re-growth of residual cancer cells starts to rise [11]. In the present study the median overall survival was 14.8 months and median time to progression was 8 months.

Few studies reported the results of the use of Gemcitabine and cisplatin in patients with metastatic breast cancer. Results from at least four phase II trials were comparable to our results. Nagourney et al. [7] had conducted a phase II trials of cisplatin and Gemcitabine in previously treated patients with MBC. The original trial of cisplatin (30 mg/m²) plus Gemcitabine (1.000 mg/m²) administered on days 1, 8 and 15 of each 28-day cycle, which was changed after patients no. 12 to cisplatin (30 mg/m²) plus Gemcitabine (750 mg/m²) days 1 and 8 of each 21-day cycle due to myelosuppression (primarily thrombocytopenic). The overall response rate of 50% had achieved. The median time to progression was 8.5 months and the median overall survival was 15.5 months for patients who were found to be sensitive *ex vivo* culture studies. The activity observed also in drug resistant patients, suggests relative non-cross resistance with other drug combination. In the second trial, Stemmler et al. [16] reported an overall response rate of 34.3%, median overall survival of 11.9 months and median time to progression was 6.1 months. The objective of this trial was to search for treatment regimens that can be used in anthracycline and taxane-pretreated patients i.e the combination of Gemcitabine and cisplatin was investigated as a salvage regimen in intensively pretreated patients with (MBC). This can explain the lower response rate in comparison to our results. The third study was conducted at Mayo Hospital, Lahore and concluded that the combination was an effective second-line regimen for patients with (MBC), after failure of anthracycline-based regimen, with overall response rate of 61.9% (8). The last trial is ongoing trials in anthracycline resistant cases after adjuvant or first line therapy for (MBC) in 43 patients, 36 were evaluable for response and 39 for toxicity. The

overall response rate was 44.4%. Median survival and time to progression have not yet been reached [17].

In spite of response rate of 54.5% that was achieved in our patients, this treatment was not curative. In such situation the quality of life is important, this good quality of life Consistent with the modest toxicity profile reported in phase I study [9]. Gemcitabine and cisplatin combination was well tolerated. Although the most common grade 3 to 4 toxicities were hematologic in nature, few neutropenia complications resulted. There was only one episode of neutropenic fever. The most frequent non hematologic adverse events were nausea and vomiting, stomatitis, renal impairment (G I & II) and fatigue. Two of three patients with renal dysfunction recovered completely, while the third patient has continued evidence of progressive renal important and discontinued further chemotherapy. The incidence of hematologic toxicity (G 3 & 4) in our patients was lower than that reported in other combination chemotherapy regimen such as Docetaxel and Antracyclin, Docetaxel and Gemcitabine, vinorelbine and Epirubicin (8% to 29%) versus (63% to 94%), (7.5% to 37%) and (50%) respectively [12,13, 14,18,19]. The modest toxicity profile of this combination regimen is a major advantage for this regimen, because it is important to balance the side effects profile and efficacy (therapeutic ratio) to optimize the management of metastatic breast cancer [20,21,22].

In conclusion, the combination of Gemcitabine and cisplatin has been shown in this study to be highly active regimen, with manageable toxicity in patients with metastatic breast cancer as first-line treatment. Our results were similar to and perhaps better than, those reported with other effective but more toxic regimens, including those combining anthracyclines and taxans and vinorelbine and epirubicin [7,14,18,19]. Further trials are warranted that use this combination in the neoadjuvant setting, where a high response rate is particularly useful.

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