Carboplatin and Weekly Paclitaxel in Metastatic and Locally Advanced Breast Cancer Patients. A Pilot Study

MOHAMAD A. HASSAN, M.D.
The Department of Clinical Oncology, Faculty of Medicine, Cairo University and Jeddah Cancer Center, Dr Erfan Hospital.

Abstract

Background: Platinum complexes are active in a wide range of solid tumors. Although both cisplatin and carboplatin have shown activity in breast cancer. However, some recent reports have demonstrated encouraging results, especially carboplatin in combination with taxanes.

Aims: To evaluate efficacy and safety of the combination of Craboplatin (C) and weekly paclitaxel (P) as first line therapy in metastatic (MBC) and locally advanced breast cancer (LBC) patients.

Patients and Methods: Twenty two patients with MBC and LBC were included. 16 patients with MBC were treated by Anthracyclines during the adjuvant phase, 3 patients had MBC as first presentation and 3 patients had LBC. All the Patients were treated with carboplatine 320mg/m$^2$ day one and paclitaxel 80mg/m$^2$ day 1 and 8, both repeated every 3 weeks until progression/refusal or for a maximum of 8 cycles. A dose reduction was made in case of grade 3 and 4 toxicities.

Results: From October 2005 to December 2007, 22 patients with LBC and MBC were included at Erfan Hospital Saudi Arabia. Median age was 49. Of 21 patients were assessed for response, two patients (9%) achieved complete remission (CR) and 12 patients (54.5%) had partial response (PR) giving an overall response rate of 63.5%. Time to disease progression (TTP) was 7.4 months. The median survival time was 18.7 (4-3 8) months. The actuarial overall survival for the first and second years were 56% and 21% respectively (Kaplan and Meier method). The most common grade 3 and 4 toxicities were neutropenia (9%), thrombocytopenia (4.5%), anemia (9%), neuropathy (9%), fatigue (9%), mucosities (9%) and myalgia (4.5%).

Conclusion: Carboplatin and Weekly paclitaxel is very effective and safe combination as first line therapy in patients with LBC and MBC.

Key Words: Breast cancer – Carboplatin – Paclitaxel.

Introduction

BREAST cancer is the most common malignancy affecting women and the second leading cause of cancer death in the U.S. Although only a small minority of patients is initially diagnosed with metastatic breast cancer, it is estimated that 20%-85% of patients depending on the initial stage will ultimately progress to metastatic disease [1]. Many different agents are used in this setting-including anthracyclines, taxanes and antimetabolites. But a single standard of care has not been identified [2].

Platinum complexes are active in a wide range of solid tumors [3]. Although both cisplatin and carboplatin have shown activity in breast cancer, carboplatin may be the more appropriate choice for treatment of MBC, because it causes less severe nonhematologic toxicities. In four phase II studies of previously untreated patients with MBC, single-agent carboplatin produced objective response rates of 20%-35% [4-7]. In three of those trials, carboplatin was administered at a fixed dose of 400mg/m$^2$ every 3 or 4 weeks or based on glomerular filtration rate to achieve an area under the concentration-versus-time curve (AUC) of 7mg/ml minute every 4 weeks in one study [8].

The rationale for combining carboplatin with a taxane is based on their single-agent activities in metastatic breast cancer, their complementary mechanisms of action and the activity of this combination in other malignancies [6,7,9,10].

Interestingly, when used in combination, paclitaxel) appears to have a platelet-sparing action that reduces the thrombocytopenia seen with carboplatin alone [11].

The aim of the present phase II trial is to further study the efficacy and safety of CP regimens in LBC and MBC patients as first line chemotherapy.

Patients and Methods

Twenty two patients older than 18 years of age with pathologically confirmed adenocarcinoma of
the breast that was locally advanced (stage III B) or metastatic (stage IV) were eligible for this study. Eastern Cooperative Oncology Group (ECOG) performance status had to be 0, 1, or 2. Adequate bone marrow and organ function were required, a negative baseline pregnancy test. Prior chemotherapy apart from adjuvant chemotherapy was not allowed, provided that the regimen did not contain a taxane and was completed at least 6 months before enrollment into this study.

Each patient gave written informed consent, and the following pretreatment evaluations were performed: Medical history, physical examination, vital signs, height and body weight and ECOG performance status. Radiological measurements (chest X-ray, abdomo-pelvic sonar or computed tomography scan and bone scan) and any other images were done when appropriate, complete blood count with differential and platelet count, hemoglobin and chemistries (AST, ALT, bilirubin, and creatinine and CA1 5.3).

Patients were treated with carboplatine 320mg/m² day one infused over 30 minute and paclitaxel 80mg/m² day 1 and 8, one hour infusion, both repeated every 3 weeks. Patients received premedication consisting of dexamethasone 20mg orally administered approximately 12 and 6 hours before paclitaxel, in addition antiemetic and H2 blocker were given for the patients. In case of grade 3 or 4 toxicity, 25% dose reduction of the 2 drugs was made in subsequent cycles. Grade 2 toxicities were managed symptomatically, if possible, with no dose reductions.

Assessment for treatment response was made according to WHO criteria, while toxicity was assessed according to NCI/CTC criteria. Treatment was continued for a maximum of 8 cycles, provided no disease progression or patient’s refusal.

The secondary efficacy end points included duration of tumor response, time to disease progression and survival. Duration of response was the interval between the date of onset of a PR or CR and the date that progressive disease occurred. Time to disease progression was the interval between the date of the start of treatment and the date of occurrence of progressive disease or the date that other antitumor therapy was started. Survival was the interval between the date of the start of treatment and the date of death. If a patient was lost to follow-up, that patient was censored as of the date of last contact.

Statistical analysis: It was a descriptive analysis. The statistical analysis was done using an IBM compatible computer and Statistics 6.0 for Windows XP statistical package. Overall survival was estimated by Kaplan Meier’s Method.

Results

Twenty two patients of (MBC and LBC) were enrolled in this study from October 2005 to December 2007; the characteristics of the patients are included in (Table 1). 16 patients received antharacycline in the adjuvant therapy. Three patients were treated as (LBC) and the other 3 patients did not receive prior chemotherapy before. 21 patients were assessed as one patient refuse to continued treatment after he received one cycle of chemotherapy.

Table (1): Characteristics of the patients.

<table>
<thead>
<tr>
<th>Patients characters</th>
<th>Total No. of patients=22</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age:</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>31-72</td>
</tr>
<tr>
<td>Median</td>
<td>49</td>
</tr>
<tr>
<td>Performance status:</td>
<td></td>
</tr>
<tr>
<td>0-1</td>
<td>9</td>
</tr>
<tr>
<td>2</td>
<td>13</td>
</tr>
<tr>
<td>Hormonal receptors:</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>14</td>
</tr>
<tr>
<td>Negative</td>
<td>7</td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
</tr>
<tr>
<td>Visceral Mets site:</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>10</td>
</tr>
<tr>
<td>Liver</td>
<td>6</td>
</tr>
<tr>
<td>Bones</td>
<td>11</td>
</tr>
<tr>
<td>Others</td>
<td>4</td>
</tr>
<tr>
<td>Locally advanced stage 111B</td>
<td>3</td>
</tr>
<tr>
<td>Prior chemotherapy:</td>
<td></td>
</tr>
<tr>
<td>Adjuvant anthracycline</td>
<td>16</td>
</tr>
<tr>
<td>Prior radiotherapy</td>
<td>11</td>
</tr>
</tbody>
</table>

Efficacy data:

The overall response among 22 patients assessed was 63.5%. Two patients (9%) achieved CR, 12 patients (54.5%) achieved PR and 2 patients (9%) had disease stability, while 5 patients (23%) progressed on treatment (Table 2).

Table (2): The assessment response among 22 patients.

<table>
<thead>
<tr>
<th>Response</th>
<th>No. of patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response</td>
<td>14</td>
<td>63.5</td>
</tr>
<tr>
<td>Complete response (CR)</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>12</td>
<td>54.5</td>
</tr>
<tr>
<td>Stable disease (SD)</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Progression disease (PD)</td>
<td>5</td>
<td>23</td>
</tr>
<tr>
<td>Not evaluated (NE)</td>
<td>1</td>
<td>4.5</td>
</tr>
</tbody>
</table>
One of three patients with LBC achieved CR and the other patient who achieved CR did not receive chemotherapy before (Fig. 1). Time to disease progression (TTP) was 7.4 months. The median survival time was 18.7 month with the range (4-38) months. The actuarial overall survival for the 1 and 2 years were 56% and 21% respectively (Kaplan and Meier method).

**Fig. (1): Before chemotherapy (A) and after 2 cycles of chemotherapy (B).**

**Treatment related toxicity:**

Neutropenia occurred in two patients (9%) only one patient had suffered febrile neutropenia (4.5%), other important grade 3-4 hematological toxicities (Table 3) were anemia in two patients (9%) and thrombocytopenia in one patient (4.5%).

Table (3): Hematological grade 3 and 4 toxicity.

<table>
<thead>
<tr>
<th>Events</th>
<th>Number of patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Aneamia</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>1</td>
<td>4.5</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>1</td>
<td>4.5</td>
</tr>
</tbody>
</table>

Non hematological grade 3-4 toxicities were neuropathy in 2 patients (9%), mucositis in 2 patients (9%) and constipation in one patient (4.5%) (Table 4). A total of 107 cycles were administered with a median of 5 cycles per patient. In 18 cycles (17%) there was 25% dose reduction of the two drugs.

Table (4): Nonhemtological grade 3 and 4 toxicity.

<table>
<thead>
<tr>
<th>Events</th>
<th>Number of patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuropathy</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Constipation</td>
<td>1</td>
<td>4.5</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1</td>
<td>4.5</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Myalgia</td>
<td>1</td>
<td>4.5</td>
</tr>
<tr>
<td>Mucositis</td>
<td>2</td>
<td>9</td>
</tr>
</tbody>
</table>

**Discussion**

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. At the present time, the optimal management of MBC remains a significant therapeutic challenge; the clinicians can use three different systemic treatment modalities for advanced breast cancer: endocrine therapy, chemotherapy and biologic targeted therapy [12].

Weekly paclitaxel regimens have been shown to provide greater dose-intensity when compared with the conventional schedules. Response rates ranging from 21.5% to 79% have been achieved in patients with locally advanced and metastatic breast cancer [9,13,15].

Response rates from 43% to 62% have been obtained with the paclitaxel and carboplatin regimen on an every-3-weeks schedule to treat advanced breast cancer [16,17].

This study confirms the activity of carboplatin and weekly paclitaxel in patients with metastatic breast cancer. The weekly dosing schedule paclitaxel 80mg/m² plus carboplatin at dose 320mg/m² is well-tolerated and does not appear to compromise antitumor activity when compared to similar phase II studies with weekly or every 3-week dosing schedules. Although the weekly paclitaxel is asso-
cated with increased clinic visits compared to the
every 3-week administration schedule, the im-
proved toxicity profile may result in improved
quality of life and should be considered in the
palliative treatment of metastatic disease.

The Hellenic Cooperative Oncology Group
(HCOG) treated 66 patients with a regimen of
paclitaxel (175mg/m² infused over 3 hours) fol-
lowed by an infusion of carboplatin (to an AUC
of 6mg/ml min over 30 minutes) [17].

Treatment was repeated every 3 weeks (q3w)
in an outpatient clinic. Eight (12%) patients
achieved complete responses and 27 (41%) patients
had partial responses for an overall response rate
of 53% (95% confidence interval [CI] = 41%-65%)
In this study carboplatin was used in fixed dose
320mg/m² and paclitaxel in weekly dose 80mg/m²
gives response rate of 63.5% and this is more
effective comparable to HCOG study used this
combination in different dose schedules this may
be as some of the patients in HCOG study received
prior chemotherapy before. Also this results are
more or comparable to the results of Fountzilas et
al. [16] and Perez et al. [10] using the regimen as
first-line therapy for advanced and metastatic
disease achieved response rates of 54% and 62%,
respectively.

As expected, the weekly administration schedule
of paclitaxel in this study ameliorated many of the
toxicities associated with paclitaxel/carboplatin
when were given in every 3 weeks. In this study
Febrile neutropenia was reported in 4.5% and grade
3/4 neutropenia was reported in 9% of patients.
And this was less than the results of Perez et al.
[10] who reported grade 3/4 neutropenia in 82% of
patients with the every 3-week paclitaxel/carboplatin
and that reported by Loesch et al. [18] in which
paclitaxel was given the weekly dose of 100mg/m².
The lower dose of paclitaxel 80mg/m² in this study
resulted in less peripheral neuropathy 9% grade
3/4. Interestingly, only 18% of the patients enrolled
in this study required dose reductions compared to
61% of patients receiving paclitaxel 100mg/m²
and carboplatin (AUC, 2) in the Loesch study.

The combined use of paclitaxel/gemcitabine
was superior to single agent paclitaxel in terms of
RR, TTP and survival [19]. Although no such study is
yet available comparing CP regimen versus
paclitaxel however it should be emphasized that
the combination of PC regimen may provide less
toxicities compared to paclitaxel monotherapy at
175 to 200mg/m² [10].

Also this combination has good activity in
patients with LBC as see in this study one out of
three patients achieved CR and the other 2 patients
achieved a good PR and this warrant further study
to use this combination as neadjuvant therapy in
LBC however The small sample size of this study
does not obviously allow for a reliable subgroup
analysis.

The notion that trastuzumab (monoclonal anti-
obodies directed against the Her2-neu receptors)
has a very strong synergistic interaction with certain
drugs especially paclitaxel and platinum salts, [20]
have prompted the evaluation of the triplet pacli-
taxel/Platinum/Trastuzumab in the treatment of
metastatic breast cancer as first line. An overall
response rate of 84%, median time to progression
of 14.2 months and median overall survival of 32.2
months was reported with this triplet combination
[21].

Conclusion:

This study supplies interesting information that
CP regimen may prove to be one of the effective
regimens in patients with metastatic and locally
advanced breast cancer, further randomized trials
are needed to verify both the benefits of adding
carboplatin, as well as the improved toxicity profile
for weekly chemotherapy or whenever the use of
anthracyclines is considered to be either too toxic
or potentially ineffective or combination of this
regimen with targeted therapy like trastuzumab in
over expressed HER-2.

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