Gemcitabine-taxane experience in the treatment of metastatic breast cancer

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KEYWORDS
Gemcitabine; Docetaxel; Paclitaxel; Combination therapy; Response rate; Toxicity; Disease markers metastatic breast cancer

Management of metastatic breast cancer (MBC) is difficult and overall response rates (ORR) resulting from anthracycline and taxane-based regimens remain modest. The antimetabolite drug gemcitabine has been shown to have high activity when used as first-line treatment of MBC, particularly when incorporated into combined therapy regimens. Gemcitabine-containing regimens have also been used successfully as salvage therapy in women with anthracycline or taxane-pretreated MBC. Phase II clinical studies have demonstrated high ORR with gemcitabine-docetaxel (ORR: 36–65.5%) and gemcitabine-paclitaxel (ORR: 40–68%) combination regimens. A highly favourable risk-benefit ratio has also been reported for gemcitabine-containing triplets such as gemcitabine-paclitaxel-epirubicin (ORR: 92%) and gemcitabine-paclitaxel-doxorubicin (ORR: 80.4%). Gemcitabine-containing regimens have a favourable toxicity profile with few serious toxic events reported. An important step forward in the evaluation of novel chemotherapeutic regimes for MBC is establishing a correlation between disease markers and response to therapy. Preliminary data suggest that there is a close relationship between HER2 extracellular domain levels (>30 ng/ml) and treatment outcome. HER2-positive patients had a lower ORR to gemcitabine-paclitaxel chemotherapy than women who were HER2-negative. Further studies to establish a link between other breast cancer markers and predicted response to treatment are warranted.

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Introduction

Metastatic breast cancer (MBC) is an incurable disease and the current goal of chemotherapy is to prevent tumour proliferation and increase long-term survival without drug resistance developing during treatment. Studies have shown that patients who achieve a complete response to first-line chemotherapy have a good chance of becoming long-term survivors [1,2]. Until recently, anthracycline and taxane-based regimens were considered the standard treatment for women with MBC. When these drugs were used as single first-line therapy, overall response rates
Table 1  Overall response rates (%) to single-agent chemotherapy in women with metastatic breast cancer

<table>
<thead>
<tr>
<th></th>
<th>First-line</th>
<th>Second-line</th>
<th>After anthracyclines + taxanes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxorubicin</td>
<td>40–50</td>
<td>32–36</td>
<td></td>
</tr>
<tr>
<td>Epirubicin</td>
<td>52–68</td>
<td>25–35</td>
<td></td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>29–63</td>
<td>19–57</td>
<td></td>
</tr>
<tr>
<td>Docetaxel</td>
<td>47–65</td>
<td>39–58</td>
<td>17</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>20–30</td>
<td>20–27</td>
<td>20</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>23–37</td>
<td>13–41</td>
<td>22</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>40–44</td>
<td>17–36</td>
<td>25</td>
</tr>
</tbody>
</table>

Results taken from [3].

(EvR) of around 40% were achieved. However, responses were considerably lower (EvR: 20–30%) when they were used as second-line/salvage treatment (Table 1) [3]. This low response associated with second-line treatment has been attributed to the widespread use of anthracyclines and taxanes as (neo)adjuvant therapy and the development of resistance to these drugs.

Over the past ten years, several new drugs have become available for the management of MBC including the antimetabolites gemcitabine and capecitabine [2]. Gemcitabine (Gemzar®; Lilly) has been shown to have good activity in MBC although the ORR achieved when this drug was used alone as first- or second-line chemotherapy were no better than the response rates achieved earlier with anthracyclines or taxanes (Table 1). Gemcitabine has a favourable toxicity profile making it a suitable candidate for combination therapy. Preclinical data suggested that gemcitabine may have synergistic activity with taxanes and this was confirmed by Alexopoulos et al. in a phase II clinical trial [4]. This paper reviews the evidence for the efficacy of gemcitabine in MBC, focussing on gemcitabine-taxane combination therapy.

<table>
<thead>
<tr>
<th>Previous docetaxel response</th>
<th>No. of patients (%)</th>
<th>Response to docetaxel plus gemcitabine</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Complete response</td>
<td>Partial response</td>
<td>Stable disease</td>
<td>Progressive disease</td>
</tr>
<tr>
<td>Stable disease</td>
<td>30 (60)</td>
<td>2 (6.7)</td>
<td>13 (43.4)</td>
<td>10 (33.3)</td>
<td>5 (16.7)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>20 (40)</td>
<td>1 (5)</td>
<td>7 (35)</td>
<td>4 (20)</td>
<td>8 (40)</td>
</tr>
<tr>
<td>Total</td>
<td>50</td>
<td>3 (6)</td>
<td>20 (40)</td>
<td>14 (28)</td>
<td>13 (26)</td>
</tr>
</tbody>
</table>

Median TTP: 15 months
Median survival: 7.5 months

Data taken from [4].

Gemcitabine-docetaxel combination therapy

The first evidence for in vivo synergy between gemcitabine and docetaxel was presented by Alexopoulos et al. following an important phase II trial in 2004 [4]. This study involved 50 women who had developed docetaxel-refractory or -resistant MBC after four cycles of docetaxel chemotherapy. When these women were treated with docetaxel (100 mg/m², day 1) combined with gemcitabine (900 mg/m², day 1, 8) every 3 weeks for a maximum of six cycles, three patients (6%) showed a complete response to combined therapy, 20 patients (40%) had a partial response (ORR: 46%) and 14 (28%) had stable disease (Table 2). Median survival (OS) was 15 months, with a median time to disease progression (TTP) of 7.5 months [4]. The observation of a complete or partial response to gemcitabine-docetaxel in women who had previously failed to respond to docetaxel chemotherapy alone was strong evidence of in vivo synergy between these two antitumour drugs.

Combination therapy with gemcitabine (2500 mg/m², day 1) plus docetaxel (65 mg/m², day 1) administered every 2 weeks has also been evaluated as first-line treatment in women with histologically-confirmed MBC, with an ORR of 66% (95% CI: 46.8–81.4; 4/51 complete responses, 17/51 partial responses) and a median TTP of more than 9 months. Twenty-two percent of patients achieved stable disease after therapy. The combination was well-tolerated and few adverse events were reported [5].

Achieving a clinical response in women who have failed or relapsed after previous chemotherapy for MBC is a specific challenge. In this setting, good response rates were achieved when gemcitabine-docetaxel was used as salvage treatment. A number of studies reported ORR of 36–65.6%, a median TTP of 8 months and median OS of 12.7–24.5 months when gemcitabine-docetaxel was used in women with pretreated MBC [6–8].
Gemcitabine-paclitaxel

Paclitaxel has been shown to increase the accumulation of gemcitabine-triphosphate, the active metabolite of gemcitabine, in in-vivo studies and preclinical data in human lung and breast cancer cell lines show that gemcitabine and paclitaxel have at least additive cytotoxicity when used in combination. These data have led to the evaluation of gemcitabine-paclitaxel as combination therapy in MBC.

Gemcitabine-paclitaxel has been evaluated as first-line chemotherapy in MBC patients, and in a phase II trial Delfino et al. demonstrated that this drug combination resulted in a higher ORR and longer TTP than gemcitabine or paclitaxel alone [9]. In this study, 45 women with metastatic disease were treated with paclitaxel (175 mg/m², day 1) plus gemcitabine (1200 mg/m², day 1, 8) every 3 weeks for a maximum of eight cycles. Analysis of treatment efficacy revealed an ORR of 68% (95% CI: 52–71%), with a mean duration of response of 18 months (95% CI: 11–26.7 months) and median TTP of 11 months (95% CI: 7.1–18.7 months). The combination was well-tolerated with no serious toxicity reported. Similar results were reported by Colomer et al. after a phase II study of biweekly gemcitabine (2500 mg/m², day 1) plus paclitaxel (150 mg/m², day 1) in 43 patients with advanced breast cancer. In this study, the ORR was 71% (95% CI: 62–81%), with 11 patients achieving a complete response. Once again the drug combination was well-tolerated and overall toxicity was low [10].

A number of phase II clinical trials have also been carried out to evaluate the efficacy of gemcitabine-paclitaxel as salvage therapy in women with relapsed MBC after anthracycline-containing regimens [11–13]. ORR in these studies ranged from 40–55%, with a median TTP of 8 months and median OS of 12 months [11–13]. Combined treatment with gemcitabine-paclitaxel has a high risk-benefit ratio and can be used successfully to manage advanced disease in heavily pretreated patients with MBC.

Gemcitabine-paclitaxel combination triplets

The excellent safety profile of gemcitabine-paclitaxel has led to attempts to increase ORR further by adding a third chemotherapeutic agent to the treatment regimen. The anthracycline drugs doxorubicin and epirubicin have been successfully combined with gemcitabine-paclitaxel and evaluated as triplet chemotherapy in a number of clinical trials.

In a phase II study carried out by Sánchez-Rovira et al., doxorubicin-gemcitabine-paclitaxel (GAT) was evaluated as first- or second-line chemotherapy in 41 women with MBC [14]. The drug triplet was administered every 2 weeks, and doxorubicin (30 mg/m², day 1) was given 16 h before gemcitabine (2500 mg/m², day 2) and paclitaxel (135 mg/m², day 2) to reduce toxicity. The drug combination was shown to have high efficacy with an ORR of 80.4% (95% CI: 68.3–92.5%). Fifteen of the 41 patients (36.6%) showed a complete response and median OS was 27 months. The triplet combination was associated with a favourable safety profile, with no significant grade 3 or 4 haematological toxicity reported [14].

Gemcitabine (1000 mg/m², day 1, 4) and paclitaxel (175 mg/m², day 1) have also been combined with epirubicin (90 mg/m², day 1) and evaluated in a phase II study of 36 women with MBC [15]. Half of these women received the drug combination as first-line chemotherapy and 50% received the combination as second-line/salvage therapy. Gemcitabine-paclitaxel-epirubicin, administered every 3 weeks for a maximum of eight cycles, was associated with an ORR of 92% (95% CI: 77.5–98.2%) and a complete response rate of 31%. Although grade 3 and 4 haematological toxicity was observed, non-haematological toxicity was mild. These authors suggested that this triplet combination should be evaluated further due to its highly favourable ORR and survival benefit (progression-free survival (PFS): 20.8 months) [15].

Phase III trials of gemcitabine-taxane combination therapy

In addition to the phase II trials reported above, gemcitabine-taxane combinations have also been evaluated in a number of phase III clinical trials. These have included a comparison of gemcitabine-paclitaxel with paclitaxel alone [16], gemcitabine-epirubicin-paclitaxel vs. 5-fluorouracil-epirubicin-cyclophosphamide [17] and gemcitabine-docetaxel vs. capecitabine-docetaxel [18].

Gemcitabine-paclitaxel vs. paclitaxel

This large, randomised, multicentre study compared gemcitabine-paclitaxel with paclitaxel alone as first-line treatment in 529 women with MBC [16]. Patients were randomised to receive single-agent paclitaxel (175 mg/m², day 1) or gemcitabine (1250 mg/m², day 1, 8) plus pacli-
gemcitabine-paclitaxel (175 mg/m², day 1), every 3 weeks until disease progression. The primary objective was OS and the secondary objectives were PFS, ORR and toxicity. Gemcitabine-paclitaxel was clearly more effective than paclitaxel alone with a hazard ratio of 0.775 (95% CI: 0.627–0.959) in favour of the combined therapy [16]. Median OS was 18.5 months (95% CI: 16.5–21.2 months) for gemcitabine-paclitaxel vs. 15.8 months (95% CI: 14.4–17.4 months) for paclitaxel alone. ORR, TTP and PFS were also significantly higher in women given the combination treatment (Table 3). The combination was well-tolerated and toxicity was similar in both arms of the study. The authors concluded that gemcitabine-paclitaxel should be considered as first-line therapy in patients with MBC.

Gemcitabine-epirubicin-paclitaxel vs. 5-fluorouracil-epirubicin-cyclophosphamide
Gemcitabine-epirubicin-paclitaxel was compared with 5-fluorouracil-epirubicin-cyclophosphamide in a multicentre, prospective, randomised phase III trial in 259 women with stage IV MBC [17]. Patients were randomly assigned to either gemcitabine (1000 mg/m², day 1, 4), epirubicin (90 mg/m², day 1) and paclitaxel (175 mg/m², day 1) (GET) or fluorouracil (500 mg/m², day 1), epirubicin (90 mg/m², day 1) and cyclophosphamide (500 mg/m², day 1) (FEC) every 21 days for eight cycles. After a median follow-up time of 20.4 months there was no significant difference in median TTP (9.1 vs. 9.0 months for GET and FEC, respectively; p = 0.557) or ORR (62.3 vs. 51.2%, respectively; p = 0.093) between the two treatment arms. However, treatment-related toxicity was higher in patients treated with GET than in those receiving FEC.

Predictive markers of clinical response
Establishing a correlation between disease markers and response to therapy would be of great value when designing clinical trials of novel therapeutic agents and drug combinations for MBC. Understanding this relationship would also help oncologists to make decisions regarding treatment, which can be individualised to a particular patient according to their marker status and predicted response to therapy. The only study to date to attempt to correlate treatment outcome with the presence of disease markers was that of Colomer et al. [10], who evaluated ORR according to baseline HER2 extracellular domain (ECD) levels assessed by ELISA. In this study patients with positive HER2 ECD status (>30 ng/mL) had a lower ORR to treatment with paclitaxel (150 mg/m²) plus gemcitabine (2500 mg/m²) than patients with negative HER2 ECD levels (Table 4). The results of this preliminary study are interesting and further work in this area is clearly warranted. It is yet to be determined how this information can benefit patients in terms of treatment choice.

The results of these phase II and III clinical studies support the use of gemcitabine-taxane combinations as first- or second-line treatment of MBC, as these regimens are associated with high ORR and a favourable toxicity profile. Further studies are warranted, particularly in the area of

<table>
<thead>
<tr>
<th>ORR (%) (95% CI)</th>
<th>Gemcitabine-paclitaxel</th>
<th>Paclitaxel</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>40.8 (34.9–46.7)</td>
<td>22.1 (17.2–27.2)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Median TTP (months) (95% CI)</td>
<td>5.2 (4.2–8.6)</td>
<td>2.9 (2.6–3.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>6-month PFS (%)</td>
<td>37</td>
<td>23</td>
<td>0.0027</td>
</tr>
</tbody>
</table>

Results taken from [16].

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>HER2 ECD status*</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (complete + partial response)</td>
<td>29</td>
<td>83%</td>
</tr>
<tr>
<td>No response</td>
<td>12</td>
<td>17%</td>
</tr>
</tbody>
</table>

*HER2 ECD positivity was based on a cut-off value of >30 ng/ml. Results taken from [10].

Table 3 Gemcitabine-paclitaxel vs. paclitaxel in the treatment of metastatic breast cancer

Table 4 Response rates according to baseline HER2 ECD levels
triplet chemotherapy where superior ORR have been achieved. However, haematological toxicity has to be monitored. Further evidence of the relationship between disease markers and response to treatment is urgently required.

References


