Gemcitabine Combination Chemotherapy in Metastatic Breast Cancer: Phase II Experience

Review Article [1] | December 01, 2003
By Joyce O'Shaughnessy, MD [2]

Gemcitabine has been evaluated in combination with paclitaxel, docetaxel, anthracyclines, vinorelbine, and cisplatin as first-line treatment and after prior chemotherapy in patients with metastatic breast cancer. Results with gemcitabine/taxane combinations have been especially encouraging, with these combinations providing promising outcomes with regard both to tumor response and tolerability. The combination of gemcitabine and paclitaxel has garnered particular interest for further phase III evaluation on the basis of high response rates and durable responses in both treatment-naive and treatment-experienced patients, including anthracycline-pretreated patients.

Gemcitabine (Gemzar) is a nucleoside antimetabolite that undergoes intracellular phosphorylation to its activated diphosphate and triphosphate forms. The triphosphate form, which is competitive with deoxycytidine-triphosphate, is incorporated into DNA, resulting in masked DNA chain termination; the diphosphate form reduces deoxycytidine triphosphate levels, resulting in increased incorporation of gemcitabine triphosphate. Gemcitabine exhibits single-agent activity in metastatic breast cancer, including in heavily pretreated patients.[1,2] The agent has been evaluated in patients with advanced breast cancer in a variety of two-drug chemotherapy combinations.[2]

Among these, the combination of gemcitabine and paclitaxel or docetaxel (Taxotere) has generated considerable interest for evaluation in phase III trials. Gemcitabine/Paclitaxel Five phase II trials have examined the gemcitabine/paclitaxel combination in advanced breast cancer (Table 1).[2-8] Among trials evaluating the combination as first-line treatment, Colomer and colleagues reported use of gemcitabine at 2,500 mg/m^2 on day 1 and paclitaxel at 150 mg/m^2 on day 1 every 14 days in 42 patients, of whom 72% had received adjuvant therapy.[3] Complete response was observed in 10 patients (24%) and partial response was observed in 19 (45%). Median response duration was 9 months. Grade 4 neutropenia occurred in 17% of patients and grade 4 leukopenia occurred in 8%. One patient developed neutropenic fever. Grade 3 thrombocytopenia, nausea/ vomiting, neurosensory toxicity, and constipation were each observed in 4% of patients. Grade 3 elevation of aspartate aminotransferase level was observed in 8% of patients. Genot et al assessed gemcitabine at 1,200 mg/m^2 on days 1 and 8 and paclitaxel at 175 mg/m^2 on day 1 every 21 days in patients who had received no previous chemotherapy for metastatic disease.[4] Among 36 evaluable patients, two (6%) had a complete response and 13 (36%) had a partial response; seven (19%) had stable disease. At the time of reporting, the median follow up was 175 days. Median response duration was 11.5 months and median time to disease progression was 7.5 months. The most frequent grade 3 hematologic toxicities were leukopenia (41 episodes) and granulocytopenia (52 episodes); 24 episodes of grade 4 granulocytopenia were observed. Delfino et al assessed gemcitabine at 1,200 mg/m^2 on days 1 and 8 and
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175 mg/m² on day 1 every 21 days in 42 evaluable patients, of whom 27 (64%) had received previous adjuvant therapy. Complete response was observed in 14% of patients and partial response in 41%; 26% of patients had stable disease. The median response duration was 19 months, median time to progressive disease was 9 months, and median time to treatment failure was 9 months. At 1 year, 65% of patients remained alive. Grade 3 or 4 toxicities consisted of leukopenia in six patients, thrombocytopenia in six patients, and mucositis in seven patients. In metastatic breast cancer patients pretreated with chemotherapy, Sanchez-Rovira et al reported findings in 44 heavily pretreated patients, of whom nearly all had previously received anthracyclines and 20% had received paclitaxel,[6] Patients received gemcitabine at 2,500 mg/m² on days 1 and 15 and paclitaxel at 135 mg/m² on days 1 and 15 every 28 days. Seven patients (16%) had a complete response and 13 (30%) had a partial response. The median response duration was 8 months (range:
4 to 26 months) and median survival was 12 months (range: 4 to 28 months). Grade 3 or 4 hematologic toxicity occurred in 15% of patients; 34% of patients required granulocyte colony-stimulating factor (G-CSF) support. In a trial reported by Murad et al, patients previously treated with an anthracycline-containing regimen were treated initially with gemcitabine at 1,000 mg/m² on days 1, 8, and 15 and paclitaxel at 175 mg/m² on day 1 every 28 days.[7] After unacceptable thrombocytopenia occurred in the first five patients treated, dosing was changed to a 21-day schedule with gemcitabine given on days 1 and 8 and paclitaxel on day 1. Five of 29 (17%) evaluable patients had a complete response and 11 (38%) had a partial response; six patients (21%) had stable disease. Median response duration was 8 months (range: 4 to 26 months) and median survival was 12 months (range: 4 to 28+ months), with 1- and 2-year survival rates of 45% and 30%, respectively. Grade 3 or 4 thrombocytopenia was observed in five (19%) of 27 cycles using the 28-day schedule compared with six (5%) of 110 cycles using the 21-day schedule ($P = 0.04$). Eight patients had grade 3 neutropenia; two had grade 4 neutropenia associated with fever, both during the 28-day treatment cycle. Two patients had grade 3 neuropathy. These findings suggest that gemcitabine/ paclitaxel is effective as first-line treatment and in pretreated patients, with high response rates and durable responses being observed. It is particularly encouraging that a high response rate was observed in anthracycline-pretreated patients, since low response rates have been reported with paclitaxel alone after anthracycline anthracycline failure. The gemcitabine/paclitaxel combination currently is being investigated as first-line therapy in metastatic breast cancer patients who have received prior anthracycline-based adjuvant therapy in a large phase III study.[8] Gemcitabine/Docetaxel Laufman and colleagues evaluated gemcitabine at 800 mg/m² on days 1, 8, and 15 plus docetaxel at 100 mg/m² on day 1 every 4 weeks as first-line treatment in 39 evaluable metastatic breast cancer patients, of whom the majority had received adjuvant anthracycline treatment (Table 1).[2,9] Objective responses were observed in 79% of patients. Granulocyte colony-stimulating factor was not used prophylactically, and grade 3 or 4 neutropenia occurred in all patients. In a study by Kornek et al, 52 patients (43 chemotherapy-naive) received gemcitabine at 1,500 mg/m² plus docetaxel at 50 mg/m² on days 1 and 15 every 4 weeks with G-CSF support.[10] Among 34 evaluable patients, the objective response rate was 59% (64% in patients receiving first-line treatment) and median time to progression was 7 months. Grade 3 or 4 neutropenia occurred in 10 patients. Pelegri et al evaluated gemcitabine 2,500 mg/m² on day 1 plus docetaxel 65 mg/m² on day 1 every 2 weeks in 36 patients, of whom less than half had received adjuvant therapy.[11] Objective responses were observed in 72% of 25 evaluable patients. Grade 3 or 4 neutropenia occurred in 13 of 29 patients evaluable for toxicity. Mavroudis et al assessed gemcitabine at 900 mg/m² on days 1 and 8 plus docetaxel at 100 mg/m² on day 8 every 3 weeks with G-CSF support in 52 patients who had relapsed following anthracycline-based chemotherapy, of whom approximately half had received prior taxane treatment.[12]
Table 2

Phase II Studies of Gemcitabine Plus Anthracyclines in Metastatic Breast Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Dose (mg/m²)</th>
<th>ORR</th>
<th>Median TTP</th>
<th>Major Grade 3 or 4 Hematologic Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perez-Manga[16] (N = 42)</td>
<td>Gemcitabine 800 d1,8,15 Doxorubicin 25 d1,8,15 q28d</td>
<td>55%</td>
<td>NA (median response duration 12 mo)</td>
<td>Grade 3/4: leukopenia 46%, neutropenia 67% of patients</td>
</tr>
<tr>
<td>Rivera[17] (N = 49)</td>
<td>Gemcitabine 800 d1,8 Pegylated liposomal doxorubicin 24 d1 q21d</td>
<td>52%</td>
<td>4.5 (median response duration 5.6 mo)</td>
<td>Grade 3/4: leukopenia 74%, thrombocytopenia 27% of patients</td>
</tr>
<tr>
<td>Campone et al[18] (N = 35)</td>
<td>Gemcitabine 1,500 d1,8 Epirubicin 75 d1 q21d in 20 patients</td>
<td>33%</td>
<td>NA</td>
<td>Grade 3/4: neutropenia 90%, thrombocytopenia 20%</td>
</tr>
<tr>
<td></td>
<td>Gemcitabine 1,250 d1,4 Epirubicin 75 d1 q21d in 15 patients</td>
<td>67%</td>
<td>NA</td>
<td>Grade 3/4: neutropenia 64% of cycles, thrombocytopenia 11% of cycles</td>
</tr>
</tbody>
</table>

NA = not available; ORR = objective response rate; TTP = time to disease progression.
Adapted from Heinemann [2]
The objective response rate was 54% (including 44% in patients with prior taxane treatment), and the median time to progression was 8 months. Grade 3 or 4 neutropenia was observed in 15 patients. Alexopoulos and colleagues assessed gemcitabine at 900 mg/m$^2$ on day 1 and 8 and docetaxel at 100 mg/m$^2$ every 3 weeks in 36 patients, of whom half had received prior anthracyclines or taxanes.[13] Objective responses were observed in 72% of patients and the median response duration was 3.2 months. Brandi et al assessed gemcitabine at 1,000 mg/m$^2$ on day 1 and 8 plus docetaxel at 80 mg/m$^2$ on day 8 every 3 weeks in 37 patients whose disease had progressed after first-line anthracycline treatment.[14] The objective response rate was 60%, and median time to progression was 6 months. Grade 3/4 neutropenia occurred in 33% of patients. In a study in 40 patients with anthracycline- resistant disease, Fountzilas et al examined a regimen of gemcitabine at 1,000 mg/m$^2$ on days 1 and 8 plus docetaxel 75 mg/m$^2$ on day 1 every 3 weeks with G-CSF support.[15] The objective response rate was 36% and the median time to progression was 7 months. Grade 3 or 4 neutropenia occurred in 19 patients. Based on these promising phase II studies, a randomized phase III study comparing docetaxel/gemcitabine to docetaxel/capecitabine is currently under way.

**Gemcitabine/A anthracyclines** Perez-Manga et al evaluated firstline gemcitabine at 800 mg/m$^2$ plus

<table>
<thead>
<tr>
<th>Study</th>
<th>Dose (mg/m$^2$)</th>
<th>ORR</th>
<th>Median TTP</th>
<th>Major Grade 3 or 4 Neutropenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haider et al[19] (N = 60)</td>
<td>Gemcitabine 1,000 d1,15,21,21 q28d</td>
<td>52%</td>
<td>8.5 mo</td>
<td>Grade 3/4 neutropenia 11 patients</td>
</tr>
<tr>
<td>Moser et al[20] (N = 38)</td>
<td>Gemcitabine 1,200 d1,8</td>
<td>30%</td>
<td>NA</td>
<td>Grade 3/4 neutropenia 7 patients</td>
</tr>
<tr>
<td>Valenza et al[21] (N = 29)</td>
<td>Gemcitabine 1,000 d1,8,15 q28d</td>
<td>48%</td>
<td>Mean time to progression 6.8+ mo</td>
<td>Grade 3 thrombocytopenia 3 patients</td>
</tr>
<tr>
<td>Nicolaides et al[22] (N = 31)</td>
<td>Gemcitabine 1,000 d1,8</td>
<td>22%</td>
<td>3.5 mo (median response duration 6 mo)</td>
<td>Grade 3/4 neutropenia 15 patients</td>
</tr>
<tr>
<td>Donadio et al[23] (N = 26)</td>
<td>Gemcitabine 1,000 d1,8</td>
<td>39%</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Gokmen et al[24] (N = 26)</td>
<td>Gemcitabine 1,200 d1,8</td>
<td>45%</td>
<td>5.5 mo</td>
<td>Grade 3 thrombocytopenia 4 patients</td>
</tr>
<tr>
<td>Mariani et al[25] (N = 31)</td>
<td>Gemcitabine 1,200 d1,8</td>
<td>22%</td>
<td>NA</td>
<td>Grade 3/4 neutropenia 15 patients</td>
</tr>
<tr>
<td>Stathopoulos et al[26] (N = 51)</td>
<td>Gemcitabine 1,000 d1,15 q28d</td>
<td>54%</td>
<td>6 mo (median response duration 6 mo)</td>
<td>Grade 3/4 neutropenia 4 patients</td>
</tr>
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NA = not available; ORR = objective response rate; TTP = time to disease progression.

Adapted from Heinemann.[2]
doxorubicin at 25 mg/m² on days 1, 8, and 15 every 4 weeks in 42 patients, of whom 29 had received adjuvant therapy (Table 2).[2,16] The objective response rate was 55% and the median response duration was 12 months. There was significant hematologic toxicity, but no grade 3 or 4 cardiotoxicity. Rivera et al treated 49 patients, of whom 27 had received adjuvant therapy, with gemcitabine at 800 mg/m² on days 1 and 8 plus pegylated liposomal doxorubicin at 24 mg/m² on day 1 every 3 weeks. Objective responses were observed in 52% of 46 evaluable patients; the median response duration was 5.6 months and the median time to progression was 4.5 months. Hematologic toxicities were the most common grade 3 or 4 toxicities; one patient previously treated with an anthracycline developed a transient decrease in left ventricular ejection fraction.[17] Campone et al assessed a regimen of gemcitabine at 1,500 mg/m² on days 1 and 8 plus epirubicin at 75 mg/m² on day 1 every 3 weeks.[2, 18] In the first 20 patients, of whom approximately half received the regimen as first-line treatment, significant doselimiting toxicities were observed and the response rate was 33%; altering the regimen to gemcitabine at 1,250 mg/m² on days 1 and 4 and epirubicin on day 1 every 3 weeks resulted in an objective response rate of 67% in 15 subsequently enrolled patients. **Gemcitabine/Vinorelbine** Haider et al evaluated gemcitabine at 1,000 mg/m² on days 1, 15, and 21 plus vinorelbine (Navelbine) at 40 mg/m² on days 1 and 21 every 4 weeks with G-CSF support in 45 patients as first-line therapy and in 15 patients as second-line therapy (prior anthracyclines in two-thirds) (Table 3).[2,19] Objective response rates were 56% in patients receiving first-line treatment and 40% in those receiving second-line treatment (52% overall) and median times to progression were 9.5 and 7 months, respectively (8.5 months overall). Grade 3 or 4 neutropenia occurred in 11 patients. Moser et al assessed gemcitabine at 1,200 mg/m² on days 1 and 8 plus vinorelbine at 25 mg/m² on days 1 and 8 every 21 days as first- or second- line treatment in 30 evaluable patients (38 evaluable for toxicity).[20] The objective response rate was 30%. Grade 3 or 4 neutropenia occurred in seven patients. Valenza et al reported a 48% response rate in 29 patients (prior anthracycline/ taxane adjuvant therapy in 25) receiving gemcitabine at 1,000 mg/m² on days 1, 8, and 15 plus vinorelbine at 25 mg/m² on days 1 and 8 every 4 weeks.[21] The objective response rate was 48% and the mean time to progression was 6.8+ months. Nicolaides et al evaluated gemcitabine at 1,000 mg/m² plus vinorelbine at 30 mg/m² on days 1 and 8 every 3 weeks in 31 patients who had received prior taxanes.[22]. Responses were observed in 22% of patients and the median time to progression was 3.5 months. Grade 3 or 4 neutropenia occurred in 15 patients. Donadio et al reported an objective response rate of 39% among 26 patients receiving gemcitabine at 1,000 mg/m² plus vinorelbine at 25 mg/m² on days 1 and 8 every 3 weeks.[23] Gokmen et al assessed gemcitabine at 1,200 mg/m² plus vinorelbine at 30 mg/m² on days 1 and 8 every 3 weeks in 26 patients as first-, second-, or third-line treatment.[24] The objective response rate was 45% in 22 evaluable patient and the median time to progression was 5.5 months. Mariani et al assessed the same regimen in 31 patients, of whom most had received anthracycline or taxane treatment.[25] The objective response rate was 22% in 27 evaluable patients. Grade 3 or 4 neutropenia occurred in 15 patients. Stathopoulos and colleagues evaluated gemcitabine at 1,000 mg/m² plus vinorelbine at 25 mg/m² on days 1 and 15 every 4 weeks in 51 patients, of whom all had received anthracyclines and half had received taxanes.[26] The objective response rate was 54% in 50 evaluable patients and the median time to progression was 6 months. Grade 3 or 4 neutropenia occurred in 4 patients.
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Gemcitabine/Cisplatin  
Calderillo-Ruiz assessed gemcitabine at 1,200 mg/m² on days 1 and 8 plus cisplatin at 75 mg/m² on day 1 every 3 weeks in 31 patients as first-line treatment (Table 4).[2,27] Objective response was observed in 80% of patients. Grade 3 or 4 neutropenia occurred in 20% of cycles. In previously treated patients, Doroshow et al examined gemcitabine at 1,000 mg/m² on days 2 and 8 plus cisplatin at 25 mg/m² on days 1 to 4 every 3 weeks in 24 patients as first- or second-line treatment and in 31 patients as third-line or subsequent treatment with G-CSF support being required in the more heavily pretreated patients.[28] The overall objective response rate was 34% (43% in 21 evaluable moderately pretreated patients and 26% in 23 evaluable heavily pretreated patients). Median times to progression were 8.3 months with first-line treatment, 3.7 months with second-line treatment, and 3.5 months with third-line or subsequent treatment. Grade 3 or 4 neutropenia occurred in 39 patients and grade 3 or 4 thrombocytopenia occurred in 38. Burch et al assessed gemcitabine at 1,000 mg/m² plus cisplatin at 25 mg/m² on days 1, 8, and 15 every 4 weeks in 21 patients, and reported an objective response rate of 29% and median time to progression of 7.1 months.[29] Grade 3 or 4 neutropenia occurred in 81% of patients and grade 3 or 4 thrombocytopenia occurred in 62%. Chaudry and colleagues assessed the same regimen in 28 patients with prior anthracycline or taxane therapy, finding an objective response rate of 39% and a median response duration of 5.3 months.[30] Grade 4 neutropenia occurred in 9% of cycles and grade 4 thrombocytopenia occurred in 12% of cycles. Galvez et al assessed gemcitabine at 1,200 mg/m² on days 1, 8, and 15 plus cisplatin at 50 mg/m² on day 1 every 4 weeks in 41 patients who had received anthracycline therapy.[31] Objective responses were observed in 49% of patients and median time to progression was 5.2 months. Grade 3 or 4 neutropenia occurred in 48% of patients and grade 3 or 4 thrombocytopenia occurred in 47%. Nagourney et al assessed gemcitabine at 1,000 mg/m² plus cisplatin at 30 mg/m² on days 1, 8, and 15 every 4 weeks (first 12 patients) and gemcitabine at 750 mg/m² plus cisplatin at 30 mg/m² on days 1 and 8 every 3 weeks (subsequent patients) in 30 patients receiving second- to sixth-line therapy.[32] Overall, the objective response rate was 50% and median time to progression was 3.5 months (5.5 months with second- or third-line treatment and 3.5 months with fourth-line or subsequent treatment). Grade 3 or 4 neutropenia occurred in 15% of cycles and grade 3 or 4 thrombocytopenia occurred in 47% of cycles.

Conclusion  
Gemcitabine shows considerable promise for use in combination with other chemotherapeutic agents as first-line or subsequent treatment for metastatic breast cancer. On the basis of these phase II studies, the combination of gemcitabine with a taxane appears to offer promise regarding both efficacy and tolerability. On the basis of its activity in early phase studies, the gemcitabine/paclitaxel combination is being evaluated as first-line treatment in a phase III trial in

Table 4  
<table>
<thead>
<tr>
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<th>Major Grade 3 or 4 Hematologic Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calderillo-Ruiz[27] (N = 31)</td>
<td>Gemcitabine 1,200 d1,8 Cisplatin 75 d1 q21d</td>
<td>80%</td>
<td>NA</td>
<td>Grade 3/4 neutropenia 20% of cycles</td>
</tr>
<tr>
<td>Doroshow et al[28] (N = 55)</td>
<td>Gemcitabine 1,000 d2,6 Cisplatin 25 d1,4 q21d</td>
<td>34%</td>
<td>3.5–8.3 mo</td>
<td>Grade 3: neutropenia in 9 patients, thrombocytopenia in 19 patients; grade 4: neutropenia in 30 patients, thrombocytopenia in 19 patients, anemia in 5 patients</td>
</tr>
<tr>
<td>Burch et al[29] (N = 21)</td>
<td>Gemcitabine 1,000 d1,8,15 Cisplatin 25 d1,8,15 q28d</td>
<td>29%</td>
<td>7.1 mo</td>
<td>Grade 3: neutropenia 38%, thrombocytopenia 24%, grade 4: neutropenia 43%, thrombocytopenia 36%</td>
</tr>
<tr>
<td>Chaudry et al[30] (N = 28)</td>
<td>Gemcitabine 1,000 d1,8,15 Cisplatin 25 d1,8,15 q28d</td>
<td>39%</td>
<td>(median response duration 5.3 mo)</td>
<td>Grade 4: neutropenia 9% of cycles, grade 4 thrombocytopenia 12% of cycles</td>
</tr>
<tr>
<td>Galvez et al[31] (N = 41)</td>
<td>Gemcitabine 1,200 d1,8,15 Cisplatin 50 mg/m² d1,4 q28d</td>
<td>49%</td>
<td>5.2 mo (median response duration 10.6 mo)</td>
<td>Grade 3/4: neutropenia 48%, thrombocytopenia 47%, anemia 42%</td>
</tr>
<tr>
<td>Nagourney et al[32] (N = 30)</td>
<td>Gemcitabine 1,350 d1,8,15 Cisplatin 30 d1,8,15 q28d (12 patients)</td>
<td>50%</td>
<td>3.5 mo</td>
<td>Grade 3: neutropenia 11% of cycles, leucopenia 17% of cycles, thrombocytopenia 33% of cycles, anemia 6% of cycles; grade 4: neutropenia 4% of cycles, thrombocytopenia 14% of cycles</td>
</tr>
</tbody>
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NA = not available; ORR = objective response rate; TTP = time to disease progression.
metastatic breast cancer, and docetaxel/ gemcitabine is being compared with
docetaxel/capecitabine. The gemcitabine/ paclitaxel combination is also being assessed in the GET
regimen (gemcitabine/epirubicin/paclitaxel) as first-line treatment in metastatic disease, and as
neoadjuvant treatment of locally advanced disease.

Disclosures: The author(s) have no significant financial interest or other relationship with the
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