Gemcitabine: monochemotherapy of breast cancer

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Background: Gemcitabine is a nucleoside analogue with proven activity in advanced and metastatic breast cancer. Its action is associated with a favourable toxicity profile which is mainly hematological. Its unique mechanism of action along with not overlapping toxicity is particularly useful both in combination treatment with other active drugs and a sequential therapy in the palliative setting.

Design: Phase II studies of gemcitabine performed over the last decade were reviewed.

Results and conclusions: Despite some conflicting results in some trials, gemcitabine confirmed to be a useful drug to treat this condition.

Key words: gemcitabine, metastatic breast cancer, phase II trials

Introduction

Despite over three decades of clinical investigation and the availability of numerous active cytotoxic agents for breast cancer chemotherapy, metastatic breast cancer remains essentially incurable in an overwhelming percentage of patients [1].

In this review we will analyze pertinent information on the activity of single agent gemcitabine mainly by discussing the results of phase II trials that have been performed over the past decade.

Gemcitabine, a nucleoside analogue (2',2'-difluorodeoxycytidine dFdC) has demonstrated experimental and clinical antitumor activity in a variety of human neoplasms, including pancreatic, ovarian, non-small-cell lung, as well as breast tumors [2, 6].

Methods

The MEDLINE database was searched for publications related to the use of gemcitabine in breast cancer, in addition to full publications, abstracts presented at the meeting of the American Society of Clinical Oncology (ASCO), the European Cancer Conference (ECCO), and the San Antonio Breast Cancer Meeting were also discussed in this study.

Results

Results of phase II studies of gemcitabine are reported (Table 1).

Carmichael et al. [7] performed the first phase II trial under these conditions:

- Forty four patients entered the study. Gemcitabine was administered at the starting dose of 800 mg/m² once every week for 3 weeks followed by one week rest.
- Seven patients had received adjuvant therapy previously and 19 had received chemotherapy of whom 17 with anthracyclines.
- The mean dose delivered per injection was 725 mg/m². The maximum dose delivered was 960 mg/m².
- Forty patients were evaluable, three achieved a complete response and seven a partial response. The overall response rate was 25.0% (95% confidence interval CI, 12.7%–41.2%). The median survival duration for all 40 evaluable patients was 11.5 months, the median response duration was 13.5 months (range 6–43 months).
- Toxic side effects were mainly hematological: WHO grade 3 neutropenia was observed in 23% and grade 4 in 7% respectively.
- Nine patients reported vomiting and 21 complained of nausea.
- Grade 4 symptomatic toxicities were infection in one patient and nausea and vomiting in one.

Possinger et al. [8] performed a phase II trial in 42 patients with locally advanced or metastatic disease. Gemcitabine was administered at the dose of 1000 mg/m² for 3 weeks every 4 weeks; the mean delivered dose was 942 mg/m².

- There were non complete responses. Authors reported 6 partial responses with an overall response rate of 14.3% (95% CI, 5.4–28.5%),
- The median overall survival was 15.2 months. Grade 3/4 toxicities were nausea and vomiting in 5 patients, diarrhea in one, hepatic enzyme elevation in 7 patients.
- Blackstein et al. [9] reported the results of a Phase II trial conducted at 3 sites in the US and Canada. They treated 39 patients, 35 were evaluable. The dose was 1200 mg/m².

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They observed 2 complete responses and 11 partial responses for an overall response rate of 37.1% (95% CI, 21.5–55.1). The median time to progression was 5.1 months (95% CI, 3.5–8.8 months). Among the 13 responders the median response duration was 8.8 months (95% CI, 5.2–12.7 months). The median survival time was 21.1 months (95% CI, 11.0–26.9 months).

They treated patients with WHO Grade 3 neutropenia in 30.3%, leukopenia in 12.1%, anemia in 9.1% and grade 3 thrombocytopenia in 6.3%. Two patients experienced grade 4 toxicities; one patient developed infection and one abnormal pulmonary function. The other grade 3 complaints were nausea and vomiting, registered in 4 patients (10.3%).

This considerable difference in terms of response rate (14 versus 37) remains unclear to date.

### Table 1. Summary of phase II studies of single-agent gemcitabine for metastatic breast cancer

<table>
<thead>
<tr>
<th>Reference</th>
<th>No/resp eval</th>
<th>Study dose</th>
<th>Treatment setting</th>
<th>Response rate</th>
<th>MTTP months</th>
<th>Duration of r</th>
<th>O.5 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carmichael et al. (1995)</td>
<td>44/40</td>
<td>800 mg/m²/day</td>
<td>1, 8 and 15 q28</td>
<td>ORR: 25% 3 CR 7 PR</td>
<td>N.R.</td>
<td>13.5</td>
<td>11.5</td>
</tr>
<tr>
<td>Possinger et al. (1999)</td>
<td>42/42</td>
<td>1000 mg/m²/day</td>
<td>1, 8 and 15 q28</td>
<td>ORR: 14.3% 0 CR 6 PR</td>
<td>N.R.</td>
<td>5.6</td>
<td>15.2</td>
</tr>
<tr>
<td>Schmid et al. (1999)</td>
<td>20/20</td>
<td>250 mg/m²/6-h</td>
<td>infusion, days 1, 8 and 15 q28</td>
<td>ORR: 25% 1 CR 4 PR</td>
<td>6.3</td>
<td>N.R.</td>
<td>51.9</td>
</tr>
<tr>
<td>Brodowicz et al. (2000)</td>
<td>25/25</td>
<td>1250 mg/m²/day</td>
<td>1, 8 and 15 q28</td>
<td>2nd-line therapy 9 pts Anthracyclines 15 pts ORR: 18%</td>
<td>N.R.</td>
<td>5.1, 3.5</td>
<td>2nd-line therapy: 12.6 3rd-line therapy: 7.5</td>
</tr>
<tr>
<td>Gerson et al. (2000)</td>
<td>19/19</td>
<td>1250 mg/m²/day</td>
<td>1, 8 and 15 q28</td>
<td>2nd-line therapy 6 pts Anthracyclines 15 pts ORR: 42%</td>
<td>NR</td>
<td>8.5</td>
<td>10.4</td>
</tr>
<tr>
<td>Valerio et al. (2001)</td>
<td>26/22</td>
<td>1000 mg/m²/day</td>
<td>1, 8 and 15 q28</td>
<td>2nd or 3rd-line therapy 26 pts ORR: 23%</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Spielmann et al. (2001)</td>
<td>47/41</td>
<td>1200 mg/m²/day</td>
<td>1, 8 and 15 q28</td>
<td>2nd-line therapy 32 pts ORR: 29% 4 CR 8 PR</td>
<td>NR</td>
<td>8.1</td>
<td>18.6</td>
</tr>
<tr>
<td>Smorenburg et al. (2001)</td>
<td>23/20</td>
<td>1200 mg/m²/day</td>
<td>1, 8 and 15 q28</td>
<td>2nd-line therapy 3 pts ORR: 0%</td>
<td>1.9</td>
<td>NR</td>
<td>7.8</td>
</tr>
<tr>
<td>Blackstein et al. (2002)</td>
<td>39/35</td>
<td>1200 mg/m²/day</td>
<td>1, 8 and 15 q28</td>
<td>1st-line therapy 39 pts Adjuvant 11 pts ORR: 37% 4 CR 9 PR</td>
<td>5.1</td>
<td>8.8</td>
<td>21.1</td>
</tr>
<tr>
<td>Modi et al. (2005)</td>
<td>22/18</td>
<td>800 mg/m²/day</td>
<td>1, 8 and 15 q28</td>
<td>2nd or 3rd-line therapy ORR: 17% 3 PR</td>
<td>9.5</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Rha et al. (2005)</td>
<td>41/38</td>
<td>850 mg/m²/day</td>
<td>1, 8 and 15 q28</td>
<td>2nd or 3rd-line therapy ORR: 20% 2 CR 6 PR</td>
<td>4.5</td>
<td>9</td>
<td>11</td>
</tr>
</tbody>
</table>

CR, Complete response; MS, Median survival; MTTP, Median time to progression; NR, not reported; ORR, Overall response rate; PR, partial response; Resp eval, Response evaluable; O.S, Overall survival.

• They observed 2 complete responses and 11 partial responses for an overall response rate of 37.1% (95% CI, 21.5–55.1). The median time to progression was 5.1 months (95% CI, 3.5–8.8 months). Among the 13 responders the median response duration was 8.8 months (95% CI, 5.2–12.7 months). The median survival time was 21.1 months (95% CI, 11.0–26.9 months).

• The treatment was associated with WHO Grade 3 neutropenia in 30.3%, leukopenia in 12.1%, anemia in 9.1% and grade 3 thrombocytopenia in 6.3%. Two patients experienced grade 4 toxicities; one patient developed infection and one abnormal pulmonary function. The other grade 3 complaints were nausea and vomiting, registered in 4 patients (10.3%).

• This considerable difference in terms of response rate (14 versus 37) remains unclear to date.

**Development of single agent gemcitabine in pretreated patients**

Brodowicz et al. [10] initiated a phase II trial with gemcitabine as single agent for second and third line cytotoxic treatment in 1994 and reported the results in 25 patients. The drug was given...
at the dose of 1250 mg/m² days 1, 8 and 15 every 28 days, as second line treatment in 9 patients and as 3rd line therapy in 16.

- Among nine patients who received gemcitabine as 2nd line there were 2 PR (22%).
- Among 16 patients who received gemcitabine as 3rd line there were 1CR (6%) one PR (6%).
- The duration of response was 5.1 months in 2nd line (range: 1.6–13.9) and 3.5 months in 3rd line (range: 1.3–10.4). The overall survival for the second line was 12.6 months (range: 3.9–30.8) and 7.5 months for the third line (range: 2.0–26.0).
- Toxicity was mainly hematological. Grade 3 anemia occurred in one (11%), grade 3 leukopenia in one (11%), grade 3 thrombocytopenia in one (11%) respectively in patients treated as 2nd line.
- In patients treated as 3rd line grade 3 anemia was observed in one patient (6%), grade 3 leukopenia in three (19%) and grade 4 thrombocytopenia was seen in four patients (25%).
- The authors concluded that the drug is active even in heavily pre-treated patients.
- Spielman et al. [11] from the Institut Gustave Roussy in Paris, reported the results of 47 patients enrolled by five French centers. The study was designed to test the safety and activity of gemcitabine as single agent in patients with metastatic disease previously treated with an anthracycline or anthraquinone regimen as first line treatment.
- Eleven patients (23%) had also previously received adjuvant therapy. Gemcitabine was given at a dosage of 1200 mg/m² on days 1, 8 and 15 followed by 1 week rest.
- Out of 41 evaluable cases, they observed 4 complete and 8 partial responses with an overall response rate of 29% (95% CI, 16–46). The median duration of response was 8.1 months (range: 2.5–27.4 months). The median survival for all 47 patients was 18.6 months (range: 0.3–42 months).
- Main toxic effects included WHO grade 3 neutropenia in 13 patients (28%), leukopenia in 8 (17%), thrombocytopenia in 3 (6%) and anemia in 2 (4%). In addition, grade 4 neutropenia occurred in one patient but was not accompanied by neutropenic fever. Grade 2 nausea and vomiting was observed in 4 patients (9%).
- One patient had a severe radiation recall reaction and one patient had a grade 3 allergic reaction. Both were withdrawn from the study.
- Schmid and colleagues [12] in an attempt to improve the efficacy of the drug tested a different schedule exploring gemcitabine in continuous infusion because the phosphorylation of the nucleoside into the active triphosphate is carried out by deoxycytidine kinase which is saturable at plasma concentrations achievable after an infusion of 30 min. They reported an overall response of 25% in a study including 20 patients, 10 of them had previously received an adjuvant therapy, 15 anthracycline treatments; the dose adopted in this trial was of 250 mg/m² in 6-h infusion.

**gemcitabine in anthracycline–taxane pre-treated patients**

Many investigators have recently studied the role of single agent gemcitabine in anthracycline and taxane pretreated patients.

- Valerio et al. [13] from the University of Palermo reported at a ASCO Meeting their results in 2001. Gemcitabine was given at the dose of 1000 mg/m² at the usual schedule. From November 1998 to August 2000 26 patients were enrolled in the study. Of the 22 patients evaluable, they reported 1 complete response (4.5%) and 4 partial responses (18.1%). As toxic effects they reported influenza-like syndrome with high temperature in 10 patients (45.4%) and fatigue in 8 (36.3%). Hematological toxicity is reported to have been negligible not requiring G-CSF support.
- Rha et al. [14] from the University of Seoul treated 41 patients with doxorubicin and paclitaxel refractory metastatic breast cancer with gemcitabine at the dose of 850 mg/m² weekly for three consecutive weeks and followed by one week rest.
- Of the 38 evaluable cases, they reported 2 complete (5.3%) and 6 partial (15.8%) remissions. Main toxic effects were represented by grade 3 neutropenia in 12 patients (29%), grade 3 anemia in 4 (10%), grade 4 anemia in one (2%), grade 3 thrombocytopenia in 5 (12%) and grade 4 thrombocytopenia in one (2%).
- The median response duration was 9 months, (range: 2–25 months). The time to progression was 4.5 months (95% CI, 3–5 months). Overall survival was 11 months (95% CI, 4–18 months).
- Smorenburg et al. [15] from Rotterdam, included in their trial 23 patients with progressive metastatic disease after previous chemotherapy that consisted either of an anthracycline followed by second line paclitaxel or docetaxel or an anthracyline–docetaxel combination.
- Eleven patients had received prior adjuvant therapy. Prior chemotherapy for metastatic disease was limited to one line in 3 patients, 14 patients had received 2 lines, 5 patients received 3 lines and one patient received 4 lines of chemotherapy before entering the trial.
- Patients received Gemcitabine at the outpatient clinic at the dose of 1200 mg/m² on day 1, 8 and 15 of a 28 day cycle. No complete or partial response was reported.
- An intention to treat analysis was performed in 23 patients: 6 patients (23%) showed stable disease with a median duration of 4 months.
- Progressive disease occurred in 13 patients within the first 2 cycles.
- The median time to progression was 1.9 months (range: 1.0–4.4) and the reported median survival was 8.1 months for the 6 patients with stable disease and 7.8 months for all patients.
- One patient stopped treatment after 4 cycles due to myalgia grade 2 and one patient stopped treatment after the second cycle because of painful erythema and induration of both legs. Other minor toxicities (grade 1 and 2) included flu-like symptoms and reversible elevations of liver enzymes.
- Neutropenia grade 3 was observed in one patient (6%), grade 3 leukopenia in three (19%) and grade 4 thrombocytopenia was seen in four patients (25%).
- From this experience authors concluded that the use of single agent gemcitabine in patients previously-treated with anthracycline and taxane was ineffective.
- Modi et al. [16] from the Memorial Sloan Kettering in New York published this year the final results of single agent...
gemcitabine as salvage treatment in patients previously treated with anthracyclines and taxanes. In order to enter the study designed to test the activity and safety of the drug in anthracycline-taxane pre-treated population patients must have received 2–4 chemotherapy regimens for breast cancer. Pre-treatment with paclixalix or doxorubicin was required as prior therapy both as adjuvant treatment or for metastatic disease. Gemcitabine was administered at the dose of 800 mg/m² weekly on days 1, 8 and 15 of each 28-day cycle.

- Out of 22 enrolled patients 18 were evaluable for response. Three patients showed a radiographic partial response, for an overall response rate of 17% (95% CI: 4–41%). In addition one patient had a minor response with a 41% reduction of liver metastases.
- Toxicity, mainly haematological, included grade 3 neutropenia in 3 patients (14%) thrombocytopenia in 2 (9%) anemia in 1 (5%).
- In addition 6 patients (27%) had elevation of their aminotransferase levels.
- Duration of response was not calculable. Median overall survival for all patients was 9.5 months (95% CI, 6.5–39.6 months).
- The authors concluded by stating that their study confirm the safety and efficacy of single agent gemcitabine as salvage treatment after anthracycline and taxanes.

**discussion**

Over the past decade more than ten Phase II trials on gemcitabine (2′,2′-difluorodeoxycytidine dFdC) in advanced or metastatic breast cancer have been published.

The clinical activity of the nucleoside analogue was first reported by Carmichael et al. in 1995 [7]. It soon appeared that gemcitabine was endowed with an interesting clinical activity associated with a favourable toxicity profile.

The drug was tested as first line in metastatic disease and in pre-treated patients. More recently the activity of the drug was particularly evaluated in patients previously treated with anthracycline and taxanes.

In chemotherapy naive patients the overall response varied from 14.3% reported by Possinger et al. [8] to 37% observed by Blackstein et al. [9]. Somewhat these conflicting results have been discussed by Heinemann [5, 6] who pointed out that the percentage of patients achieving a stable disease in Possinger study was higher than that reported by Blackstein, suggesting that after all inhibition of tumor progression might have been similar in the two studies.

In the setting of anthracycline-taxane pretreated patients, overall response varied from 23% to 0% reported by Smorenburg [15]. In this trial the extent of metastatic disease (74% of patient with visceral disease) together with the heavy pre-treatment status might at least partly explain these negative results.

As a single agent gemcitabine has confirmed its favourable toxicity profile characterized mainly by leukopenia, malaise and influenza-like symptoms. These results encourage the use of the drug in palliative care.

In the setting of anthracycline taxane-resistant cases other drugs, capecitabine and vinorelbine have proven activity.

The choice might be challenging and therapeutic consideration should include a balance between expected results and toxic effects in the individual patient.

Combination chemotherapy with gemcitabine with other drugs like doxorubicin, taxanes, vinorelbine, cisplatin and targeted therapies are presently actively pursued.

**disclosures**

Dr Ferrazzi has indicated no financial relationships with companies whose products are mentioned in this article.

**references**