Gemcitabine: A cytidine analogue active against solid tumors

YUK FUNG HUI AND JEFFREY REITZ

Abstract: The pharmacology, pharmacokinetics, clinical efficacy, adverse effects, and dosage and administration of gemcitabine are reviewed.

Gemcitabine is a deoxycytidine-analogue antimetabolite with activity against some solid tumors. Gemcitabine is phosphorylated intracellularly to difluorodeoxycytidine triphosphate, which terminates DNA-chain elongation and competitively inhibits DNA polymerase and ribonucleotide reductase. After i.v. administration, gemcitabine is rapidly distributed into total body water. The drug is deaminated in the plasma to inactive difluorodeoxycytidine; both gemcitabine and difluorodeoxycytidine are primarily renally eliminated. In clinical studies, gemcitabine reduced pain and improved function in patients with advanced pancreatic cancer. Gemcitabine has shown some activity against non-small-cell lung cancer, particularly when combined with cisplatin or ifosfamide. The agent has also shown modest activity against advanced ovarian and breast cancer. Adverse effects include dose-limiting myelosuppression, flu-like symptoms, nausea, vomiting, and rash. Gemcitabine has FDA-approved labeling for use in the treatment of locally advanced and metastatic pancreatic cancer. The recommended dosage for this indication is 1000 mg/m² (as the hydrochloride salt) i.v. given over 30 minutes weekly for seven weeks, followed after one week of rest by 1000 mg/m² i.v. given over 30 minutes weekly for three weeks every four weeks.

Gemcitabine palliates symptoms in patients with advanced or metastatic pancreatic cancer. More study is needed to determine gemcitabine's role in the treatment of non-small-cell lung cancer, ovarian cancer, and breast cancer.

Index terms: Antineoplastic agents; Dosage; Gemcitabine; Neoplasms; Pharmacokinetics; Toxicity

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Gemcitabine (2',2'-difluorodeoxycytidine) was developed as a new deoxycytidine analogue (Figure 1). This pyrimidine antimetabolite, a close relative of cytarabine, generated interest as a potential antineoplastic agent after showing activity against both RNA- and DNA-containing viruses. Gemcitabine hydrochloride was approved by the Food and Drug Administration in May 1996 for use in the treatment of advanced or metastatic pancreatic cancer.

This article reviews the pharmacology, pharmacokinetics, clinical efficacy, adverse effects, and dosage and administration of gemcitabine.
Gemcitabine Clinical Review

Pharmacokinetics

After i.v. administration, gemcitabine is rapidly distributed into total body water. In a study in which gemcitabine doses ranging from 1200 to 6400 mg/m² were infused at a fixed rate, the median distribution half-life was 6.7 minutes.7 The volume of distribution of gemcitabine is influenced by duration of infusion, age, and sex.3 When gemcitabine was infused over less than 70 minutes, the volume of distribution was 50 L/m². With longer infusions, the volume of distribution increased to 370 L/m², suggesting slowly equilibrating body compartments. Women and older patients tend to have a smaller volume of distribution than men and younger patients.

The clearance of gemcitabine is independent of the dose and the duration of infusion.3,7 Clearance among individuals is quite variable and is influenced by age and sex.3 Clearance among women is about two thirds that in men; this may be related to lower deoxycytidine monophosphate deaminase activity in women. Since the clearance of gemcitabine is unaffected by infusion duration, and since the volume of distribution increases with longer infusions, the elimination half-life increases when gemcitabine is infused over a longer period. The elimination half-life ranges from 32 to 94 minutes during short infusions and from 245 to 638 minutes during long infusions.8

Gemcitabine is metabolized in the plasma to the inactive product 2'2'-difluorodeoxyuridine by cytidine deaminase (Figure 2).7 A maximum difluorodeoxyuridine concentration is usually noted 5–15 minutes after the end of the infusion.7,9 Elimination of difluorodeoxyuridine is biphasic, with an initial half-life of 23.5–27 minutes and a terminal half-life of 50–90 minutes.7

Figure 1. Structures of gemcitabine and cytarabine.

Figure 2. Activation and metabolism of gemcitabine. dCMP = deoxycytidine monophosphate, dCTP = deoxycytidine triphosphate, dFdC = difluorodeoxycytidine, dFdCMP = difluorodeoxycytidine monophosphate, dFdCDP = difluorodeoxycytidine diphosphate, dFdCTP = difluorodeoxycytidine triphosphate, dFdU = difluorodeoxyuridine, dFdUMP = difluorodeoxyuridine monophosphate, NDP = nucleoside diphosphate, dashed arrow = stimulation, dashed arrow with X = inhibition.
minutes and a terminal half-life of 14–22.4 hours. Urinary excretion of gemcitabine and difluorodeoxyuridine accounts for more than 99% of the excreted gemcitabine dose. Only a median of 5% of a gemcitabine dose is eliminated unchanged in the urine.

Once gemcitabine enters the cell, it is phosphorylated to its active form, difluorodeoxycytidine triphosphate. The amount of intracellular difluorodeoxycytidine triphosphate resulting from a dose of gemcitabine varies among individuals and is influenced by the infusion rate. Grunewald et al. reported that the intracellular difluorodeoxycytidine triphosphate peak was observed within 30 minutes after the end of a 30-minute gemcitabine infusion and increased with the gemcitabine dose up to 350 mg/m², which corresponded to a plasma gemcitabine concentration of 15–20 µM.

At doses above 350 mg/m², the accumulation of difluorodeoxycytidine triphosphate appeared to plateau, suggesting that the intracellular transport or phosphorylation of gemcitabine is saturable.

Grunewald and coworkers also looked at the cellular pharmacokinetics of this metabolite in a study in which gemcitabine was infused at a constant rate of 10 mg/m²/min. In all patients who received gemcitabine doses up to 2400 mg/m², intracellular difluorodeoxycytidine triphosphate concentrations increased linearly with the dose. Of the 14 patients with assessable pharmacokinetics, 7 exhibited biphasic elimination and the rest a monophasic pattern. In patients with biphasic elimination, the median initial half-life was 152 minutes (range, 10–570 minutes), whereas the terminal-phase half-life was 544 minutes (range, 42–720 minutes). The median half-life for the patients with monophasic elimination was 275 minutes (range, 42–570 minutes). Variation among the patients was considerable, and no relationship between the elimination pattern and the gemcitabine dose could be discerned.

Clinical efficacy

Gemcitabine has shown activity against a variety of solid tumors, including pancreatic, colorectal, lung, head and neck, ovarian, urothelial, breast, and renal cancer. There is also a report of a positive response in leukemia. This article focuses on the use of gemcitabine in pancreatic, non-small-cell lung, ovarian, and breast cancer.

Pancreatic cancer. Pancreatic cancer is the fifth leading cause of cancer-related death in America; an estimated 27,800 people died of the disease in 1996. The five-year survival rate is less than 5%. The only curative treatment is surgical resection; however, not many patients with pancreatic cancer are candidates for resection because about 90% of them have metastases at the time of diagnosis.

Antineoplastic drugs have had only a limited role in the treatment of pancreatic cancer. In combination with radiation therapy, fluorouracil can improve the survival of individuals with localized disease. However, patients with advanced pancreatic adenocarcinoma derive minimal benefit from chemotherapy. Of more than 30 agents evaluated for efficacy in the treatment of advanced disease, only ifosfamide, fluorouracil, and mitomycin produce response rates greater than 20%. Responses to chemotherapy have generally been partial in advanced disease, and chemotherapy does not confer any survival benefit. Thus, chemotherapy is palliative in advanced pancreatic cancer.

Clinical trials of gemcitabine in patients with advanced pancreatic adenocarcinoma are summarized in Table 1. Gemcitabine had minimal activity against this type of cancer.

Table 1.
Summary of Clinical Studies of Gemcitabine in Pancreatic Cancer

<table>
<thead>
<tr>
<th>Reference</th>
<th>Regimen</th>
<th>Response Rate (%)</th>
<th>Stable Disease (%)</th>
<th>Clinical Benefit (%)</th>
<th>Median Duration of Response or Survival (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>Gemcitabine 800–1500 mg/m²/wk × 3 wk q 4 wk&lt;sup&gt;b&lt;/sup&gt;</td>
<td>44</td>
<td>11 (11/0)</td>
<td>32</td>
<td>NA&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>22</td>
<td>Gemcitabine &gt;800 mg/m²/wk × 3 wk q 4 wk with dosage escalation</td>
<td>32</td>
<td>6.3 (6.3/0)</td>
<td>18.8</td>
<td>NA</td>
</tr>
<tr>
<td>23</td>
<td>Gemcitabine 1000 mg/m²/wk × 7 wk, then 1 wk rest, then 1000 mg/m²/wk × 3 wk q 4 wk</td>
<td>63</td>
<td>NA</td>
<td>NA</td>
<td>27</td>
</tr>
<tr>
<td>24&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Gemcitabine 1000 mg/m²/wk × 7 wk, then 1 wk rest, then 1000 mg/m²/wk × 3 wk q 4 wk Fluorouracil 600 mg/m²/wk</td>
<td>Total of 126</td>
<td>NA</td>
<td>NA</td>
<td>23.8</td>
</tr>
<tr>
<td>25&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Gemcitabine 1000 mg/m²/wk × 3 wk q 4 wk plus cisplatin 50 mg/m² on days 1 and 15 q 4 wk</td>
<td>27</td>
<td>17 (17/0)</td>
<td>52</td>
<td>NA</td>
</tr>
</tbody>
</table>

<sup>a</sup>Objective response rate (partial response rate/complete response rate).

<sup>b</sup>As the hydrochloride salt.

<sup>c</sup>NA = not available.

<sup>d</sup>Reported in abstract form only.
malignancy. The median partial response rates (no complete responses were observed) were 6.3% and 11% among patients with advanced disease who completed at least two cycles of treatment.11,22

Despite these low objective response rates, both chemotherapy-naive patients and those who have failed to respond to standard single-agent therapy with fluorouracil can derive symptomatic benefit from gemcitabine. One fourth to one third of patients have at least a 50% reduction in pain and the need for analgesics and at least a 20-point improvement in the Kamofsky performance score for at least one month.23

For palliation of symptoms, gemcitabine may be superior to fluorouracil.24 In a randomized, open-label comparison of these two medications in 126 chemotherapy-naive patients with advanced pancreatic cancer, 23.8% of gemcitabine-treated patients derived clinical benefit from treatment, compared with 4.8% of fluorouracil-treated patients. However, gemcitabine was associated with higher frequencies of neutropenia and GI toxicity (23% versus 5% and 15% versus 10%, respectively).

Gemcitabine was used with cisplatin in 27 patients with advanced pancreatic adenocarcinoma; the partial response rate for this combination was 17%.25 Not surprisingly, myelosuppression was more pronounced than with gemcitabine as monotherapy.

Non-small-cell lung cancer. About 177,000 Americans were diagnosed with lung cancer in 1996.20 Lung cancer can be divided histologically into small-and non-small-cell types. The non-small-cell form is less responsive to chemotherapy than the small-cell type. Until the past few years, no single agent consistently produced objective responses in more than 25% of patients with advanced non-small-cell lung cancer (NSCLC), and none has prolonged the survival of these patients.26 Of the various agents tried in patients with NSCLC, the most active single agents are cisplatin, ifosfamide, mitomycin, and vinorelbine; response rates have ranged from 14% to 20%.27-30 The prognosis of patients with advanced NSCLC improved after the introduction of paclitaxel. In one study, paclitaxel produced a response rate of 42% in patients with stage IV NSCLC.31

Gemcitabine has been widely tested in patients with inoperable NSCLC. The results are summarized in Table 2. The dosages used in these trials were similar to those used in the pancreatic cancer trials. Patients were started on 800–1250 mg/m² i.v. (as the hydrochloride salt) infused over 30 minutes once weekly for three weeks in a four-week cycle, with dose escalation as tolerated.13,32-36 The overall response rate ranged from 14% to 58%; in two trials a small complete response rate was reported (3% and 2%).

Because of the mild toxicity associated with gemcitabine, the starting dosage was increased in some trials. An ongoing dose-defining study showed that 1750 mg/m²/wk for three weeks in a four-week cycle was close to the maximum tolerable dosage; patients were showing hepatotoxicity and myelosuppression.37 Flu-like symptoms, hepatotoxicity, and GI symptoms were seen when gemcitabine was given twice weekly at 90 mg/m².38 Even though the response rate was similar to that for the once-weekly schedule, gemcitabine was not as well tolerated. On the other hand, gemcitabine was reported to be well tolerated when given as a 24-hour instead of 30-minute infusion in an attempt to increase efficacy.39 The worst toxicity reported was grade 3 neutropenia. The response rate was 14%, comparable to that in other trials.

The mild myelotoxicity of gemcitabine prompted investigators to use it together with other myelosuppressive agents. Impressive partial response rates ranging from 22% to 58% and modest toxicity were reported when gemcitabine was used with cisplatin or ifosfamide. These data suggest that combination therapy involving gemcitabine deserves further evaluation in patients with NSCLC.

Ovarian cancer. It is estimated that 1 in 70 women will have ovarian cancer during her lifetime.49 An estimated 14,800 deaths caused by ovarian cancer in 1996 makes this cancer the fifth leading cause of cancer-related death in women.20

As with other solid tumors, surgical resection remains the best treatment for ovarian cancer. However, surgical intervention may not be feasible for patients with advanced disease. Chemotherapy is often used in these patients. Platinum-based regimens are commonly prescribed for advanced ovarian cancer; response rates as high as 70% have been reported.50-52 But the response usually lasts less than eight months. Among patients who fail to respond to platinum-based therapy, 20–40% may respond to paclitaxel.53-55 Some clinicians consider a combination of a platinum-based agent (cisplatin or carboplatin) and paclitaxel the treatment of choice for advanced ovarian cancer.56 Other agents that have shown activity against ovarian cancer are ifosfamide, altretamine, etoposide, fluorouracil, tamoxifen, and gemcitabine.16,57

Table 3 summarizes clinical trials investigating the safety and efficacy of gemcitabine in ovarian cancer patients. In all but one of the trials, gemcitabine (800–1250 mg/m²/wk once weekly for three weeks every four weeks) was given to patients who had shown resistance to platinum-based therapy.16,58-60 Dose escalation was not used. Modest activity and mild toxicity were reported, but no complete responses were observed. Underhill et al.61 tested gemcitabine in chemotherapy-naive patients with advanced epithelial ovarian cancer. The preliminary response rate in this ongoing trial is comparable to that observed in the studies that enrolled patients in whom platinum-based therapy had failed.

Further studies are needed to evaluate the safety and efficacy of combination regimens involving gemcitab-
Table 2. Summary of Clinical Studies of Gemcitabine in Non-Small-Cell Lung Cancer

<table>
<thead>
<tr>
<th>Reference</th>
<th>Regimen</th>
<th>No. Patients</th>
<th>Response Rate (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Improved Symptoms (%)</th>
<th>Median Duration of Response or Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>Gemcitabine 800–1000 mg/m²/wk × 3 wk q 4 wk&lt;sup&gt;c&lt;/sup&gt; with dose escalation</td>
<td>82</td>
<td>20 (20/0)</td>
<td>70</td>
<td>7 mo</td>
</tr>
<tr>
<td>32&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Gemcitabine 800–1250 mg/m²/wk × 3 wk q 4 wk with dose escalation</td>
<td>332</td>
<td>20 (NA&lt;sup&gt;d&lt;/sup&gt;)</td>
<td>26–63</td>
<td>8.1–9.2 mo</td>
</tr>
<tr>
<td>33</td>
<td>Gemcitabine 1000 mg/m²/wk × 3 wk q 4 wk with dose escalation</td>
<td>84</td>
<td>20(17/3)</td>
<td>NA</td>
<td>12.7 mo</td>
</tr>
<tr>
<td>34&lt;sup&gt;c,e&lt;/sup&gt;</td>
<td>Gemcitabine 1000–1250 mg/m²/wk × 3 wk q 4 wk</td>
<td>74</td>
<td>14 (14/0)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>35</td>
<td>Gemcitabine 1250 mg/m²/wk × 3 wk q 4 wk with dose escalation</td>
<td>151</td>
<td>21.8 (19.8/2)</td>
<td>22–77</td>
<td>8.8 mo</td>
</tr>
<tr>
<td>36&lt;sup&gt;c,e&lt;/sup&gt;</td>
<td>Gemcitabine 1250 mg/m²/wk × 3 wk q 4 wk</td>
<td>36</td>
<td>36 (36/0)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>37&lt;sup&gt;c,e&lt;/sup&gt;</td>
<td>Gemcitabine 1000–2800 mg/m²/wk × 3 wk q 4 wk</td>
<td>31</td>
<td>26 (26/0)</td>
<td>NA</td>
<td>8.3 mo</td>
</tr>
<tr>
<td>38</td>
<td>Gemcitabine 90 mg/m² twice weekly with dose escalation</td>
<td>86</td>
<td>19 (19/0)</td>
<td>NA</td>
<td>7.2 mo</td>
</tr>
<tr>
<td>39&lt;sup&gt;c,e&lt;/sup&gt;</td>
<td>Gemcitabine 10–180 mg/m² infused over 24 hr × 3 wk q 4 wk</td>
<td>21</td>
<td>14 (NA)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>40</td>
<td>Gemcitabine 1000 mg/m²/wk plus cisplatin 25 mg/m²/wk × 3 wk q 4 wk</td>
<td>47</td>
<td>30 (30/0)</td>
<td>NA</td>
<td>16 wk</td>
</tr>
<tr>
<td>41&lt;sup&gt;c,e&lt;/sup&gt;</td>
<td>Gemcitabine 1000 mg/m²/wk × 3 wk q 4 wk plus cisplatin 100 mg/m² on day 1 q 4 wk</td>
<td>30</td>
<td>42 (NA)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>42&lt;sup&gt;c,e&lt;/sup&gt;</td>
<td>Gemcitabine 1000 mg/m²/wk × 3 wk q 4 wk plus cisplatin 60–100 mg/m² on day 15 q 4 wk</td>
<td>66</td>
<td>38 (38/0)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>43&lt;sup&gt;c,e&lt;/sup&gt;</td>
<td>Gemcitabine 1000 mg/m²/wk × 3 wk q 4 wk plus cisplatin 100 mg/m² on day 1 q 4 wk</td>
<td>46</td>
<td>58 (56/2)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>44&lt;sup&gt;c,e&lt;/sup&gt;</td>
<td>Gemcitabine 1250 mg/m²/wk × 3 wk q 4 wk plus cisplatin 80 mg/m² on day 1 q 4 wk</td>
<td>27</td>
<td>22.2 (22.2/0)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>45&lt;sup&gt;c,e&lt;/sup&gt;</td>
<td>Etoposide 80 mg/m² on days 1–3 q 4 wk</td>
<td>27</td>
<td>22.2 (22.2/0)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>46&lt;sup&gt;c,e&lt;/sup&gt;</td>
<td>Gemcitabine 1000 mg/m²/wk × 3 wk q 4 wk plus cisplatin 100 mg/m² on day 1 q 4 wk</td>
<td>53</td>
<td>51 (NA)</td>
<td>NA</td>
<td>13 mo</td>
</tr>
<tr>
<td>47&lt;sup&gt;c,e&lt;/sup&gt;</td>
<td>Gemcitabine 1500 mg/m²/wk × 3 wk q 4 wk plus cisplatin 30 mg/m²/wk × 3 wk q 4 wk</td>
<td>20</td>
<td>30 (30/0)</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

<sup>a</sup>Objective response rate (partial response rate/complete response rate).
<sup>b</sup>As the hydrochloride salt.
<sup>c</sup>Reported in abstract form only.
<sup>d</sup>NA = not available.
<sup>e</sup>Study is ongoing.

Gemcitabine in ovarian cancer patients, including patients who are chemotherapy naive.

**Breast cancer.** Gemcitabine has shown activity against locally advanced or metastatic breast cancer. In clinical studies, gemcitabine used as a single agent yielded complete response rates of 0–8% and partial response rates of 17.5–37.5% (Table 4).<sup>18,62,63</sup> Gemcitabine has also been tested in combination with doxorubicin and epirubicin (Table 4).<sup>64,65</sup> An 83% overall response rate was reported for gemcitabine plus doxorubicin. More study is indicated.

**Adverse effects**

Gemcitabine is generally well tolerated. The adverse effects that have been reported in clinical trials are summarized in Table 5. The dose-limiting toxicity of gemcitabine, like that of other antimetabolites, is myelosuppression. Mild and transient neutropenia, thrombocytopenia, and anemia have been observed. The use of colony-stimulating factors in patients receiv-
ing gemcitabine has not been studied, but, given the mild myelosuppression associated with gemcitabine, colony-stimulating factors are generally not required. Nausea and vomiting occur frequently but are severe in only 15% of patients or less.8 Patients usually respond to standard antiemetics, such as metoclopramide.33 Transient rashes are reported during gemcitabine therapy and tend to be macular, erythematous, and pruritic. They can be managed symptomatically with topical corticosteroids or systemic antihistamines.9,23 The rashes usually remain stable or improve with continued gemcitabine therapy. Alopecia is less frequent than with some other antineoplastic medications.

Flu-like symptoms are common. In one study, all patients reported flu-like symptoms.11 Symptoms like low-grade fever, fatigue, malaise, myalgia, and arthralgia usually start the evening after gemcitabine infusion and last up to several days. These flu-like symptoms can be relieved by acetaminophen.11 High doses of gemcitabine may lead to intolerable flu-like symptoms in some patients and necessitate a reduction in the dosage.

A number of other nonhematologic toxicities may be associated with gemcitabine. In addition to the adverse effects listed in Table 5, proteinuria, hematuria, hypotension, and bronchospasm have been observed.66 These effects are usually mild and resolve within 24 hours after the infusion.

**Dosage and administration**

The optimal dosage regimen for gemcitabine has yet to be defined. A dosage regimen often evaluated has been 800–1250 mg/m² i.v. infused over 30 minutes once weekly for up to seven weeks, followed after a week of rest by 1250 mg/m² once weekly for three weeks every 28 days. Previously untreated patients may be able to tolerate higher dosages.33,67,68

The dosage regimen defined in the approved product labeling for patients with pancreatic cancer is 1000 mg/m² i.v. (as the hydrochloride salt) once a week for up to seven weeks, followed after a week of rest by 1000 mg/m² once weekly for three weeks every 28 days. The dose is infused over 20 minutes. This regimen is similar to those used in the Phase II and Phase III trials of the drug for advanced pancreatic cancer, NSCLC, and ovarian and breast cancers (Tables 1–4). No guidelines are

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**Table 3. Summary of Clinical Studies of Gemcitabine in Ovarian Cancer**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Gemcitabine Regimen</th>
<th>No. Patients</th>
<th>Response Rate (%)</th>
<th>Stable Disease (%)</th>
<th>Median Duration of Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>800 mg/m²/wk × 3 wk q 4 wk</td>
<td>42</td>
<td>19 (19/0)</td>
<td>NA</td>
<td>8.1 mo</td>
</tr>
<tr>
<td>58</td>
<td>800 mg/m²/wk × 3 wk q 4 wk</td>
<td>7</td>
<td>29 (29/0)</td>
<td>28</td>
<td>NA</td>
</tr>
<tr>
<td>59</td>
<td>800–1250 mg/m²/wk × 3 wk q 4 wk</td>
<td>13</td>
<td>15 (NA)</td>
<td>15</td>
<td>7–9 mo</td>
</tr>
<tr>
<td>60</td>
<td>1250 mg/m²/wk × 3 wk q 4 wk</td>
<td>22</td>
<td>28 (21/7)</td>
<td>36</td>
<td>NA</td>
</tr>
<tr>
<td>61</td>
<td>1250 mg/m²/wk × 3 wk q 4 wk</td>
<td>19</td>
<td>16 (16/0)</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

*aAs the hydrochloride salt.

*bObjective response rate (partial response rate/complete response rate).

*cNA = not available.

*dReported in abstract form only.

**Table 4. Summary of Clinical Studies of Gemcitabine in Breast Cancer**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Regimen</th>
<th>No. Patients</th>
<th>Response Rate (%)</th>
<th>Stable Disease (%)</th>
<th>Median Duration of Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td>Gemcitabine 800 mg/m²/wk × 3 wk q 4 wk with dosage escalation</td>
<td>40</td>
<td>25 (17.5/7.5)</td>
<td>NA</td>
<td>11.5 mo</td>
</tr>
<tr>
<td>62</td>
<td>Gemcitabine 1200 mg/m²/wk × 3 wk q 4 wk</td>
<td>26</td>
<td>46 (38.5/7.7)</td>
<td>34.6</td>
<td>NA</td>
</tr>
<tr>
<td>63</td>
<td>Gemcitabine 1000 mg/m²/wk × 3 wk q 4 wk</td>
<td>33</td>
<td>18 (18/0)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>64</td>
<td>Gemcitabine 800–1000 mg/m²/wk × 3 wk q 4 wk plus doxorubicin hydrochloride 25 mg/m²/wk × 3 wk q 4 wk</td>
<td>6</td>
<td>83 (16.7/66.7)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>65</td>
<td>Gemcitabine 1000 mg/m²/wk × 3 wk q 4 wk plus epirubicin hydrochloride 10–20 mg/m²/wk × 3 wk q 4 wk with dosage escalation</td>
<td>12</td>
<td>25 (25/0)</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

*aObjective response rate (partial response rate/complete response rate).

*bAs the hydrochloride salt.

*cNA = not available.

*dReported in abstract form only.
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Table 5. Frequency of World Health Organization (WHO) Grade 3–4 Adverse Effects Associated with Gemcitabine

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Frequency (%)</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>6–51</td>
<td>13, 23, 32, 35, 36, 42, 59</td>
</tr>
<tr>
<td>Anemia</td>
<td>1–14</td>
<td>13, 16, 23, 35, 58</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0.2–51</td>
<td>13, 16, 23, 32, 33, 35, 37, 38, 40, 42, 58, 59</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>5–53</td>
<td>11, 13, 16, 22, 23, 32, 33, 38, 42, 58, 60</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1–36</td>
<td>11, 23, 33, 35</td>
</tr>
<tr>
<td>Flu-like symptoms(^a)</td>
<td>23–100</td>
<td>11, 13, 16, 32, 33, 37, 38, 58</td>
</tr>
<tr>
<td>Alopecia</td>
<td>0–23</td>
<td>11, 13, 22, 32, 33, 42</td>
</tr>
<tr>
<td>Rash</td>
<td>0–25</td>
<td>11, 13, 32, 58</td>
</tr>
<tr>
<td>Pruritus</td>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td>Injection-site discomfort</td>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>1–22</td>
<td>13, 16, 32–34, 37, 38</td>
</tr>
<tr>
<td>Elevated transaminases</td>
<td>1–23</td>
<td>13, 16, 32, 33, 35, 37, 38, 42</td>
</tr>
<tr>
<td>Fever</td>
<td>0–32</td>
<td>13, 16, 23, 33, 38, 42</td>
</tr>
<tr>
<td>Edema(^a)</td>
<td>26–58</td>
<td>13, 16, 38</td>
</tr>
<tr>
<td>Lethargy(^a)</td>
<td>23–38</td>
<td>13, 32, 59</td>
</tr>
<tr>
<td>Dyspnea(^a)</td>
<td>0–19</td>
<td>13, 16, 38</td>
</tr>
<tr>
<td>Mucositis</td>
<td>0–1</td>
<td>13, 33</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>1</td>
<td>33</td>
</tr>
</tbody>
</table>

\(^a\)Not rated according to the WHO grades.

available on adjusting the dosage in patients with renal or hepatic insufficiency.

The fact that the rate of formation of the active metabolite of gemcitabine, difluoro(deoxy)cytidine triphosphate, is saturable suggests that the rate of infusion of gemcitabine is important. A prolonged infusion may increase systemic exposure to the triphosphate metabolite. There is interest in evaluating a prolonged infusion of gemcitabine (a five-day per week regimen and a twice-weekly regimen).38,69 However, administration more frequently than once weekly may be associated with a higher risk of toxicity.

**FDA-approved indication**

Gemcitabine carries FDA-approved labeling for use as first-line treatment in patients with locally advanced or metastatic pancreatic adenocarcinoma. It is the first agent on the U.S. market labeled for use in the treatment of pancreatic cancer.

**Use in pregnancy and in pediatric patients**

Gemcitabine is embryotoxic in rabbits and belongs in pregnancy category D. Patients should be warned of the potential hazard to the fetus if gemcitabine is considered for use during pregnancy.

Pediatric patients were not included in any of the clinical studies of gemcitabine. The safety and effectiveness of this agent have not been established for the pediatric population.

**Availability**

Gemcitabine (Gemzar, Eli Lilly & Company) is available as a lyophilized powder in vials containing 200 mg or 1 g of gemcitabine as the hydrochloride salt. After reconstitution with 0.9% sodium chloride injection to a concentration of 40 mg/mL, it can be administered as prepared or further diluted with saline to concentrations as low as 0.1 mg/mL.

**Stability and compatibility**

When prepared as directed, gemcitabine is stable in solution for 24 hours at room temperature. Reconstituted gemcitabine should not be refrigerated, as crystallization may occur.

The compatibility of gemcitabine with other drugs has not been studied. The manufacturer reported that no incompatibilities were observed when gemcitabine was put in infusion bottles or in polyvinyl chloride bags and administration sets.

**Conclusion**

Gemcitabine effectively palliates symptoms in patients with advanced or metastatic pancreatic cancer. Additional comparative Phase III trials are required to determine the role of gemcitabine in the treatment of NSCLC, ovarian cancer, and breast cancer.

**References**

38. Selzter V, Vogl S, Kaplan B. Recurrent ovarian carcinoma: retreatment utilizing combination chemotherapy including cis-diaminodichloroplatinum in patients previously re-
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