Conventional cytotoxic chemotherapy works primarily by interfering with the division and growth of cells, including cancer cells and normal tissue. However, because it is nonselective, cytotoxic chemotherapy can damage healthy cells and can cause severe side effects. Recognizing this challenge, drug developers have been looking for new ways to deliver chemotherapy to address clinical and pharmacologic challenges in the administration of intravenous (IV) cytotoxic drugs, and selectively target cancer cells to improve clinical outcomes and reduce severe adverse events.

Although newer formulations can reduce the risk for adverse events to patients, the majority of IV chemotherapies are packaged such that they require pharmacists to manipulate these drugs before administration. For example, some chemotherapies are manufactured as powder in sterile single-use vials. This powder is reconstituted with a diluent and then transferred to an infusion bag before use. Risks for contamination and medication errors are inherent in this process.

Infugem Approved as a New Formulation of Gemcitabine

On July 18, 2018, the US Food and Drug Administration (FDA) approved a novel, ready-to-use, premixed formulation of the IV cytotoxic chemotherapy gemcitabine (Infugem; Sun Pharma) for several indications, including (1) in combination with carboplatin for the treatment of advanced ovarian cancer that relapsed ≥6 months after platinum-based therapy; (2) in combination with paclitaxel for first-line treatment of metastatic breast cancer that did not respond to anthracycline-containing adjuvant chemotherapy, unless anthracycline drugs were clinically contraindicated; (3) in combination with cisplatin for first-line treatment of inoperable, locally advanced or metastatic non–small-cell lung cancer (NSCLC); and (4) for first-line treatment of locally advanced or metastatic adenocarcinoma of the pancreas after treatment with fluorouracil.

“The availability of gemcitabine in ready-to-infuse bags is a welcome development, simplifying the complex delivery of this vital chemotherapy,” said Leff Lombardo, PharmD, BCOP, Research Assistant Professor, Center of Integrated Global Biomedical Sciences, University of Buffalo, NY.

Gemcitabine was first approved by the FDA in 1996 under the trade name Gemzar, and then in 2010 as a generic drug.

Infugem is an alcohol-free, clear, colorless, sterile solution of 10 mg/mL gemcitabine in 0.9% sodium chloride that is supplied in ready-to-infuse bags as a Spike & Go package.

Mechanism of Action

Gemcitabine kills cells that are dividing. Specifically, it blocks the progression of cells through the cell growth or synthesis phase of cell division. Gemcitabine is metabolized by nucleoside kinases through a complex cellular process. After the gemcitabine nucleotide is incorporated into DNA, only one more nucleotide is added to the growing DNA strands, which eventually leads to apoptotic cell death.

Dosing and Administration

Infugem is delivered via IV infusion only. Each premixed IV infusion bag of Infugem contains 10 mg/mL of gemcitabine in 0.9% sodium chloride. Infugem is avail-
able as premixed bags with doses of 1200 mg, 1300 mg, 1400 mg, 1500 mg, 1600 mg, 1700 mg, 1800 mg, 1900 mg, 2000 mg, and 2200 mg. These bags are ready for IV infusion and do not require further preparation.6

The recommended doses of Infugem in patients with breast cancer, ovarian cancer, NSCLC, or pancreatic cancer are listed in Table 1. Dose modifications are recommended in patients with myelosuppression, based on the specific tumor type.6

Infugem can be stored at room temperature for 2 years. By contrast, the other gemcitabine formulations must be reconstituted and/or diluted for patient use and are stable at room temperature for 24 hours after preparation.8

Table 1 Infugem Dose and Schedule for Breast, Ovarian, Pancreatic, and Lung Cancer

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Infugem dose</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer</td>
<td>Infugem</td>
<td>1250 mg/m2 30 min on days 1 and 8 of each 21-day cycle</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>1000 mg/m2</td>
<td>30 min on days 1 and 8 of each 21-day cycle.</td>
</tr>
<tr>
<td>Non-small-cell lung cancer</td>
<td>1000 mg/m2</td>
<td>30 min on days 1, 8, and 15 of each 28-day cycle</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>1250 mg/m2</td>
<td>30 min on days 1 and 8 of each 21-day cycle.</td>
</tr>
</tbody>
</table>

Source: Infugem (gemcitabine in sodium chloride injection) prescribing information; July 2018.

Table 2 Efficacy of Gemcitabine in Clinical Trials

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Patient population</th>
<th>Key efficacy findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced ovarian cancer</td>
<td>356 women with advanced ovarian cancer that had relapsed ≥6 months after first-line platinum-based therapy</td>
<td>Adding gemcitabine to carboplatin significantly improved PFS and ORR  No significant difference in OS between the treatment arms</td>
</tr>
<tr>
<td>Metastatic breast cancer</td>
<td>529 women who received initial treatment for metastatic breast cancer or adjuvant/neoadjuvant anthracycline chemotherapy</td>
<td>Adding gemcitabine to paclitaxel significantly reduced disease progression and increased ORR vs paclitaxel alone  No significant difference in OS between treatment arms</td>
</tr>
<tr>
<td>Locally advanced or metastatic NSCLC</td>
<td>522 patients with inoperable advanced or metastatic NSCLC who had not received chemotherapy</td>
<td>The addition of gemcitabine to cisplatin led to significant improvement in OS, PFS, and ORR vs cisplatin alone</td>
</tr>
<tr>
<td>Locally advanced or metastatic pancreatic cancer</td>
<td>139 patients with advanced or metastatic pancreatic cancer who had not received chemotherapy</td>
<td>Gemcitabine significantly increased the clinical response, OS, and time to disease progression vs fluorouracil and doxorubicin  No confirmed objective responses reported in either treatment arm</td>
</tr>
<tr>
<td>Locally advanced or metastatic pancreatic cancer</td>
<td>126 patients with locally advanced or metastatic pancreatic cancer who had not received chemotherapy</td>
<td>Gemcitabine significantly increased the clinical response, OS, and time to disease progression vs fluorouracil and doxorubicin  No confirmed objective responses reported in either treatment arm</td>
</tr>
</tbody>
</table>

NSCLC indicates non–small-cell lung cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

Adverse Events

The most common (≥20%) adverse reactions associated with single-agent gemcitabine are nausea and vomiting, anemia, hepatic transaminitis, neutropenia, increased alkaline phosphatase levels, proteinuria, fever, hematuria, rash, thrombocytopenia, dyspnea, and peripheral edema.6

Clinical Trials

New clinical studies, including bioequivalence studies, were not needed to support the FDA approval of Infugem.9 Infugem approval was based on the safety and efficacy data that were used to approve Gemzar, as well as supportive literature data. A virtual 2-way crossover clinical trial provided additional evidence of bioequivalence between the 2 formulations.9

Table 2 summarizes the efficacy data supporting Infugem use.6

Contraindications

The use of gemcitabine is contraindicated in patients with known hypersensitivity to gemcitabine.6

Use in Specific Populations

Gemcitabine can cause fetal harm when administered to a pregnant woman; females of reproductive potential should use effective contraception during treatment with Infugem and for 6 months after the last dose. Male patients with female partners of reproductive potential should use effective contraception during and for 3 months after the last dose of Infugem.6

Women should not breastfeed during treatment with Infugem and for at least 1 week after the last dose.6

The safety and effectiveness of gemcitabine have not been established in children.6

No overall differences in safety were observed with gemcitabine as a single agent between patients aged ≥65 years and younger patients, with the exception of a higher rate of severe thrombocytopenia in older patients.6 In women with ovarian cancer who received gemcitabine combined with carboplatin in a clinical trial, the efficacy was similar between older and younger women, but the rate of severe neutropenia was higher in women aged ≥65 years.6

Warnings and Precautions

In clinical trials evaluating the maximum tolerated dose of gemcitabine, prolonging the gemcitabine infusion time beyond 60 minutes or giving it more than once weekly resulted in increased clinically significant hypotension, severe flulike symptoms, myelosuppression, and asthenia.6

Neutropenia, thrombocytopenia, and anemia occur...
with gemcitabine monotherapy and in combination with other cytotoxic drugs.\(^6\)

Pulmonary toxicity, including interstitial pneumonitis, pulmonary fibrosis, pulmonary edema, and adult respiratory distress syndrome, has been reported with gemcitabine therapy and can be fatal.\(^6\)

Patients who receive gemcitabine can have hemolytic uremic syndrome, including fatalities from renal failure or the requirement for dialysis.\(^6\)

**Infugem is the first FDA-approved formulation of gemcitabine that is packaged in a ready-to-administer, premixed bag to help prevent overdosing or underdosing of gemcitabine.**

Drug-induced liver injury, including liver failure and death, has been observed with gemcitabine, alone or in combination with other drugs; administering gemcitabine in patients with liver metastases or a history of hepatitis, alcoholism, or liver cirrhosis can exacerbate underlying hepatic insufficiency.\(^6\)

Gemcitabine should not be used together with radiation therapy or ≤7 days apart. Life-threatening mucositis, especially esophagitis and pneumonitis, has been observed with gemcitabine therapy; excessive toxicity has not been observed when gemcitabine is administered >7 days before or after radiation.\(^6\)

Capillary leak syndrome can occur in patients receiving gemcitabine as a single agent or in combination with other chemotherapeutic agents.\(^6\)

Posterior reversible encephalopathy syndrome can occur in patients receiving gemcitabine as a single agent or in combination with other chemotherapeutic drugs.\(^6\)

**Conclusion**

Infugem is the first FDA-approved formulation of gemcitabine that is packaged in a ready-to-administer, premixed bag to help prevent overdosing or underdosing of gemcitabine, improve clinical outcomes and overcome barriers to the use of cytotoxic chemotherapies, and reduce the risk for contamination for healthcare providers. Infugem is the only gemcitabine formulation that does not require reconstitution and syringe withdrawal before administration. By eliminating these steps, Infugem reduces the complexity and risks associated with other IV chemotherapy drugs.

**References**