

APPROVED

By Kim Andersen at 4:23 pm, Sep 02, 2010

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Gemtacin for injection, USP safely and effectively. See full prescribing information for Gemtacin for injection, USP. Gemtacin (gemtacin hydrochloride) for Injection, Powder, Lyophilized, For Solution For Intravenous Use Initial U.S. Approval: 1996

INDICATIONS AND USAGE

Gemtacin is indicated for the treatment of patients with:

- Ovarian Cancer in combination with carboplatin (1.1)
- Breast Cancer in combination with paclitaxel (1.2)
- Non-Small Cell Lung Cancer in combination with cisplatin (1.3)
- Pancreatic Cancer as a single agent (1.4)

DOSE AND ADMINISTRATION

Gemtacin for injection, USP is for intravenous use only.

- Ovarian: 1000 mg/m² over 30 minutes on Days 1 and 8 of each 21-day cycle (2.1)
- Breast Cancer: 1250 mg/m² over 30 minutes on Days 1 and 8 of each 21-day cycle (2.2)
- Non-Small Cell Lung Cancer: 4-week schedule, 1000 mg/m² over 30 minutes on Days 1, 8, and 15 of each 28-day cycle; 3-week schedule, 1250 mg/m² over 30 minutes on Days 1 and 8 of each 21-day cycle (2.3)
- Pancreatic: 1000 mg/m² over 30 minutes once weekly for up to 7 weeks (or until toxicity necessitates reducing or holding a dose), followed by a week of rest treatment. Subsequent cycles should consist of infusions once weekly for 3 consecutive weeks out of every 4 weeks (2.4)

Dose Reductions or discontinuation may be needed based on toxicities (2.1-2.4)

DOSE FORMS AND STRENGTHS

- 2 g vial for injection (3)

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

- 1.1 Ovarian Cancer
- 1.2 Breast Cancer
- 1.3 Non-Small Cell Lung Cancer
- 1.4 Pancreatic Cancer

2 DOSE AND ADMINISTRATION

- 2.1 Ovarian Cancer
- 2.2 Breast Cancer
- 2.3 Non-Small Cell Lung Cancer
- 2.4 Pancreatic Cancer
- 2.5 Preparation and Administration Precautions
- 2.6 Preparation for Intravenous Infusion Administration

3 DOSE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Infusion Time
- 5.2 Hematology
- 5.3 Pulmonary Toxicity
- 5.4 Hepatic
- 5.5 Pregnancy
- 5.6 Laboratory Tests
- 5.7 Radiation Therapy

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
- 6.2 Post-Marketing Experience

7 DRUG INTERACTIONS

CONTRAINDICATIONS

Patients with a known hypersensitivity to Gemtacin (4)

WARNINGS AND PRECAUTIONS

- Infusion time and dose frequency: Increased toxicity with infusion time <30 minutes or dose frequency >2 times weekly (5.1)
- Hematology: Monitor for myelosuppression, which can be dose-limiting (5.2, 5.3)
- Pulmonary toxicity: Discontinue gemtacin immediately for severe pulmonary toxicity (5.3)
- Renal: Monitor renal function prior to initiation of therapy and periodically thereafter. Use with caution in patients with renal impairment. Cases of hemolytic uremic syndrome (HUS) and/or renal failure, some fatal, have occurred. Discontinue gemtacin for HUS or severe renal toxicity (5.4)
- Hepatic: Monitor hepatic function prior to initiation of therapy and periodically thereafter. Use with caution in patients with hepatic impairment. Serious hepatotoxicity, including liver failure and death, have occurred. Discontinue gemtacin for severe hepatic toxicity (5.5)
- Pregnancy: Can cause fetal harm. Advise women of potential risk to the fetus (5.6, 8.1)
- Radiation toxicity: May cause severe and life-threatening toxicity (5.8)

ADVERSE REACTIONS

The most common adverse reactions for the single-agent (20%) are nausea and vomiting, anemia, ALT, AST, neutropenia, leukopenia, alkaline phosphatase, prothrombin, fever, hematuria, rash, thrombocytopenia, dyspnea (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Hospira, Inc. at 1-800-441-4100 or electronically at ProductComplaintsPP@hospira.com, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

PATIENT COUNSELING INFORMATION

See 17 for PATIENT COUNSELING INFORMATION

8 USE IN SPECIFIC POPULATIONS

- 8.1 Nursing Mothers
- 8.2 Pediatric Use
- 8.3 Geriatric Use
- 8.6 Renal
- 8.7 Hepatic
- 8.8 Gender

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacokinetics
- 12.3 Pharmacodynamics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

- 14.1 Ovarian Cancer
- 14.2 Breast Cancer
- 14.3 Non-Small Cell Lung Cancer (NSCLC)
- 14.4 Pancreatic Cancer
- 14.5 Other Clinical Studies

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

- 16.1 How Supplied
- 16.2 Storage and Handling

17 PATIENT COUNSELING INFORMATION

- 17.1 Low Blood Cell Counts
- 17.2 Pregnancy
- 17.3 Nursing Mothers

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Ovarian Cancer

Gemtacin in combination with carboplatin is indicated for the treatment of patients with advanced ovarian cancer that has relapsed at least 6 months after completion of platinum-based therapy.

1.2 Breast Cancer

Gemtacin in combination with paclitaxel is indicated for the first-line treatment of patients with metastatic breast cancer after failure of prior anthracycline-containing adjuvant chemotherapy, unless anthracyclines were clinically contraindicated.

1.3 Non-Small Cell Lung Cancer

Gemtacin is indicated in combination with cisplatin for the first-line treatment of patients with inoperable, locally advanced (Stage IIIA or IIIB), or metastatic (Stage IV) non-small cell lung cancer.

1.4 Pancreatic Cancer

Gemtacin is indicated as first-line treatment for patients with locally advanced (nonresectable Stage II or Stage III) or metastatic (Stage IV) adenocarcinoma of the pancreas. Gemtacin is indicated for patients previously treated with 5-FU.

2 DOSE AND ADMINISTRATION

Gemtacin for injection, USP is for intravenous use only. Gemtacin for injection, USP may be administered on an outpatient basis.

2.1 Ovarian Cancer

Gemtacin should be administered intravenously at a dose of 1000 mg/m² over 30 minutes on Days 1 and 8 of each 21-day cycle. Carboplatin AUC 4 should be administered intravenously on Day 1 after gemtacin administration. Patients should be monitored prior to each dose with a complete blood count, including differential counts.

Patients should have an absolute granulocyte count \geq 1500 \times 10⁹/L and a platelet count \geq 100,000 \times 10⁹/L prior to each cycle.

Dose Modifications

Gemtacin dosage adjustments for hematological toxicity is based on the granulocyte and platelet counts taken on Day 8 of therapy. If marrow suppression is detected, gemtacin dosage should be modified according to the guidelines in Table 2.

Table 2: Day 8 Dose Reduction Guidelines for Gemtacin in Combination with Carboplatin

Absolute granulocyte count ($\times 10^9/L$)	Platelet count ($\times 10^9/L$)	% of full dose
≥ 1500	and $\geq 100,000$	100
1000-1499	and/or 75,000-99,999	50
<1000	and/or <75,000	Hold

In general, for severe (Grade 3 or 4) non-hematological toxicity, except nausea/vomiting, therapy with gemtacin should be held or decreased by 50% depending on the judgment of the treating physician. For paclitaxel dosage adjustment, see manufacturer's prescribing information.

2.2 Breast Cancer

Gemtacin should be administered intravenously at a dose of 1250 mg/m² over 30 minutes on Days 1 and 8 of each 21-day cycle. Paclitaxel should be administered at 175 mg/m² on Day 1 as a 3-hour intravenous infusion before gemtacin administration. Patients should be monitored prior to each dose with a complete blood count, including differential counts. Patients should have an absolute granulocyte count \geq 1500 \times 10⁹/L and a platelet count \geq 100,000 \times 10⁹/L prior to each cycle.

Dose Modifications

Gemtacin dosage adjustments for hematological toxicity is based on the granulocyte and platelet counts taken on the day of therapy. Patients receiving gemtacin should be monitored prior to each dose with a complete blood count (CBC), including differential and platelet counts. If marrow suppression is detected, therapy should be modified or suspended according to the guidelines in Table 3. For cisplatin dosage adjustment, see manufacturer's prescribing information.

2.3 Non-Small Cell Lung Cancer

Two schedules have been investigated and the optimum schedule has not been determined (see Clinical Studies (14.2)). With the 4-week schedule, gemtacin should be administered intravenously at 1000 mg/m² over 30 minutes on Days 1, 8, and 15 of each 28-day cycle. Cisplatin should be administered intravenously at 100 mg/m² on Day 1 after the infusion of gemtacin. With the 3-week schedule, gemtacin should be administered intravenously at 1250 mg/m² over 30 minutes on Days 1 and 8 of each 21-day cycle. Cisplatin at a dose of 100 mg/m² should be administered intravenously after the infusion of gemtacin on Day 1. See prescribing information for cisplatin administration and hydration guidelines.

Dose Modifications

dosage adjustments for hematologic toxicity may be required for gemtacin and for cisplatin. Gemtacin dosage adjustment for hematological toxicity is based on the granulocyte and platelet counts taken on the day of therapy. Patients receiving gemtacin should be monitored prior to each dose with a complete blood count (CBC), including differential and platelet counts. If marrow suppression is detected, therapy should be modified or suspended according to the guidelines in Table 3. For cisplatin dosage adjustment, see manufacturer's prescribing information.

Dose adjustment for gemtacin in combination with carboplatin for subsequent cycles is based upon observed toxicity. The dose of gemtacin in subsequent cycles should be reduced to 800 mg/m² on Days 1 and 8 in case of any of the following hematologic toxicities:

- Absolute granulocyte count $<$ 500 \times 10⁹/L for more than 5 days
- Absolute granulocyte count $<$ 100 \times 10⁹/L for more than 3 days
- Feverish neutropenia
- Platelets $<$ 25,000 \times 10⁹/L
- Cycle delay of more than one week due to toxicity

If any of the above toxicities occur after the initial dose reduction, for the subsequent cycle, gemtacin should be given on Day 1 only at 800 mg/m².

2.2 Breast Cancer

Gemtacin should be administered intravenously at a dose of 1250 mg/m² over 30 minutes on Days 1 and 8 of each 21-day cycle. Paclitaxel should be administered at 175 mg/m² on Day 1 as a 3-hour intravenous infusion before gemtacin administration. Patients should be monitored prior to each dose with a complete blood count, including differential counts. Patients should have an absolute granulocyte count \geq 1500 \times 10⁹/L and a platelet count \geq 100,000 \times 10⁹/L prior to each cycle.

Dose Modifications

Gemtacin dosage adjustments for hematological toxicity is based on the granulocyte and platelet counts taken on Day 8 of therapy. If marrow suppression is detected, gemtacin dosage should be modified according to the guidelines in Table 2.

Table 2: Day 8 Dose Reduction Guidelines for Gemtacin in Combination with Carboplatin

Absolute granulocyte count ($\times 10^9/L$)	Platelet count ($\times 10^9/L$)	% of full dose
≥ 1500	and $\geq 100,000$	100
1000-1199	and/or 50,000-99,999	75
700-999	and/or <50,000	50
<700	and/or <50,000	Hold

In general, for severe (Grade 3 or 4) non-hematological toxicity, except alopecia and nausea/vomiting, therapy with gemtacin should be held or decreased by 50% depending on the judgment of the treating physician. For paclitaxel dosage adjustment, see manufacturer's prescribing information.

2.3 Non-Small Cell Lung Cancer

Two schedules have been investigated and the optimum schedule has not been determined (see Clinical Studies (14.2)). With the 4-week schedule, gemtacin should be administered intravenously at 1000 mg/m² over 30 minutes on Days 1, 8, and 15 of each 28-day cycle. Cisplatin should be administered intravenously at 100 mg/m² on Day 1 after the infusion of gemtacin. With the 3-week schedule, gemtacin should be administered intravenously at 1250 mg/m² over 30 minutes on Days 1 and 8 of each 21-day cycle. Cisplatin at a dose of 100 mg/m² should be administered intravenously after the infusion of gemtacin on Day 1. See prescribing information for cisplatin administration and hydration guidelines.

Dose Modifications

dosage adjustments for hematologic toxicity may be required for gemtacin and for cisplatin. Gemtacin dosage adjustment for hematological toxicity is based on the granulocyte and platelet counts taken on the day of therapy. Patients receiving gemtacin should be monitored prior to each dose with a complete blood count (CBC), including differential and platelet counts. If marrow suppression is detected, therapy should be modified or suspended according to the guidelines in Table 3. For cisplatin dosage adjustment, see manufacturer's prescribing information.

In general, for severe (Grade 3 or 4) non-hematological toxicity, except alopecia and nausea/vomiting, therapy with gemtacin plus cisplatin should be held or decreased by 50% depending on the judgment of the treating physician. During combination therapy with cisplatin, serum creatinine, serum potassium, serum calcium, and serum magnesium should be carefully monitored (see Dosage and Administration (2.3)).

2.4 Pancreatic Cancer

Gemtacin should be administered by intravenous infusion at a dose of 1000 mg/m² over 30 minutes once weekly for up to 7 weeks (or until toxicity necessitates reducing or holding a dose), followed by a week of rest from treatment. Subsequent cycles should consist of infusions once weekly for 3 consecutive weeks out of every 4 weeks.

Dose Modifications

Dosage adjustment is based upon the degree of hematologic toxicity experienced by the patient (see Warnings and Precautions (5.2)). Clearance in women and the elderly is reduced and women are somewhat less able to progress to subsequent cycles (see Warnings and Precautions (5.2))

Patients receiving gemtacin should be monitored prior to each dose with a complete blood count (CBC), including differential and platelet count. If marrow suppression is detected, therapy should be modified or suspended according to the guidelines in Table 3.

Table 3: Dose Reduction Guidelines

Absolute granulocyte count ($\times 10^9/L$)	Platelet count ($\times 10^9/L$)	% of full dose
≥ 1000	and $\geq 100,000$	100
500-999	or 50,000-99,999	75
<500	or <50,000	Hold

Laboratory evaluation of renal and hepatic function, including transaminases and serum creatinine, should be performed prior to initiation of therapy and periodically thereafter. Gemtacin should be administered with caution in patients with evidence of significant renal or hepatic impairment as there is insufficient information from clinical studies to allow clear dose recommendation for these patient populations.

Patients treated with gemtacin who completed an entire cycle of therapy may have the dose for subsequent cycles increased by 25%, provided that the absolute granulocyte count (AGC) and platelet nadirs exceed 1500 \times 10⁹/L and 100,000 \times 10⁹/L, respectively, and if non-hematologic toxicity has not been greater than WHO Grade 1. If patients tolerate the subsequent course of gemtacin at the increased dose, the dose for the next cycle can be further increased by 25%, provided again that the AGC and platelet nadirs exceed 1500 \times 10⁹/L and 100,000 \times 10⁹/L, respectively, and that non-hematologic toxicity has not been greater than WHO Grade 1.

2.5 Preparation and Administration Precautions

Caution should be exercised in handling and preparing gemtacin solutions. The use of gloves is recommended. If gemtacin solution contacts the skin or mucosa, immediately wash the skin thoroughly with soap and water or rinse the mucosa with copious amounts of water. Although acute dermal irritation has not been observed in animals, 2 of 3 rabbits exhibited drug-related systemic toxicities (death, hypoactivity, nasal discharge, shallow breathing) due to dermal absorption.

Procedures for proper handling and disposal of anti-cancer drugs should be considered. Several guidelines on this subject have been published (see References (16)).

2.6 Preparation for Intravenous Infusion Administration

The recommended diluent for reconstitution of Gemtacin for Injection, USP is 0.9% Sodium Chloride Injection without preservatives. Due to solubility considerations, the maximum concentration for gemtacin upon reconstitution is 6.40 mg/mL. Reconstitution at concentrations greater than 6.40 mg/mL may result in incomplete dissolution, and should be avoided. To reconstitute, add 50 mL of 0.9% Sodium Chloride Injection to the 2 g vial. Shake to dissolve. This dilution yields a gemtacin concentration of 38 mg/mL, which includes accounting for the displacement volume of the lyophilized powder (2.6 mL for the 2 g vial). The total volume upon reconstitution will be 52.6 mL. Complete withdrawal of the vial contents will provide 2 g of gemtacin, respectively. The appropriate amount of drug may be administered as prepared or further diluted with 0.9% Sodium Chloride Injection to concentrations as low as 0.1 mg/mL. Reconstituted Gemtacin for Injection, USP is a clear and colorless to light straw-colored solution. After reconstitution with 0.9% Sodium Chloride Injection, the pH of the resulting solution lies in the range of 2.7 to 3.3. The solution should be inspected visually for particulate matter and discoloration, prior to administration, whenever solution or container permit. If particulate matter or discoloration is found, do not administer.

When prepared as directed, gemtacin solutions are stable for 24 hours at controlled room temperature 20° to 25°C (68° to 77°F) (see USP Controlled Room Temperature). Discard unused portion. Solutions of reconstituted gemtacin should not be refrigerated, as crystallization may occur.

The compatibility of gemtacin with other drugs has not been studied. No incompatibilities have been observed with infusion bottles or polyvinylchloride bags and administration sets.

3 DOSE FORMS AND STRENGTHS

Gemtacin for Injection, USP is a white to off-white lyophilized powder available in sterile single-use vials containing 2 g gemtacin.

4 CONTRAINDICATIONS

Gemtacin is contraindicated in those patients with a known hypersensitivity to the drug.

5 WARNINGS AND PRECAUTIONS

Patients receiving therapy with gemtacin should be monitored closely by a physician experienced in the use of cancer chemotherapeutic agents.

5.1 Infusion Time

Caution - Prolongation of the infusion time beyond 60 minutes and more frequent than weekly dosing have been shown to increase toxicity (see Clinical Studies (14.5)).

5.2 Hematology

Gemtacin can suppress bone marrow function as manifested by leukopenia, thrombocytopenia, and anemia (see Adverse Reactions (6.1)), and myelosuppression is usually the dose-limiting toxicity. Patients should be monitored for myelosuppression during therapy. (see Dosage and Administration (2.1, 2.2, 2.3, and 2.4))

5.3 Pulmonary

Pulmonary toxicity has been reported with the use of gemtacin. In cases of severe lung toxicity, gemtacin therapy should be discontinued immediately and appropriate supportive care measures instituted (see Adverse Reactions (6.1 and 6.2)).

5.4 Renal

Hemolytic Uremic Syndrome (HUS) and/or renal failure have been reported following one or more doses of gemtacin. Renal failure leading to death or requiring dialysis, despite discontinuation of therapy, has been reported. The majority of the cases of renal failure leading to death were due to HUS (see Adverse Reactions (6.1 and 6.2)).

Gemtacin should be used with caution in patients with preexisting renal impairment as there is insufficient information from clinical studies to allow clear dose recommendation for these patient populations. (see Use in Specific Populations (8.7))

5.5 Hepatic

Serious hepatotoxicity, including liver failure and death, has been reported in patients receiving gemtacin alone or in combination with other potentially hepatotoxic drugs (see Adverse Reactions (6.1 and 6.2)).

Gemtacin should be used with caution in patients with preexisting hepatic insufficiency as there is insufficient information from clinical studies to allow clear dose recommendation for these patient populations. Administration of gemtacin in patients with concurrent liver metastases or a preexisting medical history of hepatitis, alcoholism, or liver cirrhosis may lead to exacerbation of the underlying hepatic insufficiency. (see Use in Specific Populations (8.7))

5.6 Pregnancy

Gemtacin can cause fetal harm when administered to a pregnant woman. In pre-clinical studies in mice and rabbits, gemtacin was teratogenic, embryocidal, and fetotoxic. There was no adequate and well-controlled studies of gemtacin in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. (see Use in Specific Populations (8.1))

5.7 Laboratory Tests

Patients receiving gemtacin should be monitored prior to each dose with a complete blood count (CBC), including differential and platelet count. Suspension or modification of therapy should be considered when marrow suppression is detected. (see Dosage and Administration (2.1, 2.2, 2.3, and 2.4))

Laboratory evaluation of renal and hepatic function should be performed prior to initiation of therapy and periodically thereafter (see Dosage and Administration (2.4)).

5.8 Radiation Therapy

A pattern of tissue injury typically associated with radiation toxicity has been reported in association with concurrent and non-concurrent use of gemtacin.

Non-concurrent (given $>$ 7 days apart) - Analysis of the data does not indicate enhanced toxicity with dose-limiting toxicity is administered more than 7 days before or after radiation, other than radiation recall. Data suggest that gemtacin can be started after the acute effects of radiation have resolved or at least one week after radiation.

Concurrent (given together or $<$ 7 days apart) - Pre-clinical and clinical studies have shown that gemtacin has radiosensitizing activity. Toxicity associated with this multimodality therapy is dependent on many different factors, including the gemtacin, frequency of gemtacin administration, dose of radiation, radiation planning technique, the target tissue, and target volume. In a single trial, where gemtacin at a dose of 1000 mg/m² was administered concurrently for up to 3 consecutive weeks with therapeutic thoracic radiation to patients with non-small cell lung cancer, significant toxicity in the form of severe, and potentially life-threatening mucositis, especially esophagitis and pneumonitis was observed, particularly in patients receiving large volumes of radiotherapy (median treatment volumes 4795 cm³). Subsequent studies have been reported and suggest that gemtacin administered at lower doses with concurrent radiotherapy has predictable and less severe toxicity. However, the optimum regimen for safe administration of gemtacin with therapeutic doses of radiation has not yet been determined in all tumor types.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Most adverse reactions are reversible and do not need to result in discontinuation, although doses may need to be withheld or reduced.

Gemtacin has been used in a wide variety of malignancies, both as a single-agent and in combination with other cytotoxic drugs.

Single-Agent Use

Myelosuppression is the principal dose-limiting toxicity with gemtacin therapy. Dosage adjustments for hematologic toxicity are frequently needed (see Dosage and Administration (2.1, 2.2, 2.3, and 2.4)).

The data in Table 4 are based on 979 patients receiving gemtacin as a single-agent administered weekly as a 30-minute infusion for treatment of a wide variety of malignancies. The gemtacin starting doses ranged from 800 to 1250 mg/m². Data are also shown for the subset of patients with pancreatic cancer treated in 5 clinical studies. The frequency of all grades and severe (WHO Grade 3 or 4) adverse reactions were generally similar in the single-agent safety databases of 579 patients and the subset of patients with pancreatic cancer. Adverse reactions reported in the single-agent safety database resulted in discontinuation of gemtacin therapy in about 10% of patients. In the comparative trial in pancreatic cancer, the discontinuation rate for adverse reactions was 14.3% for the gemtacin arm and 4.8% for the 5-FU arm. All WHO-grade laboratory adverse reactions (2.1, 2.2, 2.3, and 2.4), regardless of causality, are listed in Table 4.

In the gemtacin plus cisplatin versus etoposide plus cisplatin study, dose adjustments occurred with 20% of gemtacin injections and 16% of cisplatin injections in the gemtacin plus cisplatin arm compared with 20% of etoposide injections and 15% of cisplatin injections in the etoposide plus cisplatin arm. With a median of 5 cycles of gemtacin plus cisplatin treatment, 48% of patients experienced 15 hospitalizations due to possibly treatment-related adverse reactions. With a median of 4 cycles of etoposide plus cisplatin treatment, 18 of 66 patients (27%) experienced 22 hospitalizations due to possibly treatment-related adverse reactions. In patients who completed more than one cycle, dose adjustments were reported in 81% of the gemtacin plus cisplatin patients, compared with 68% on the etoposide plus cisplatin arm.

Study discontinuations for possibly treatment-related adverse reactions occurred in 14% of patients on the gemtacin plus cisplatin arm and in 8% of patients on the etoposide plus cisplatin arm. The incidence of myelosuppression was increased in frequency with gemtacin plus cisplatin treatment (~98% compared to that with the gemtacin monotherapy (~60%). With combination therapy, gemtacin dosage adjustments for hematologic toxicity were required more often while cisplatin dose adjustments were less frequently required.

Table 5 presents the safety data from the gemtacin plus cisplatin versus etoposide plus cisplatin non-comparative trial in pancreatic cancer. The NCI Common Toxicity Criteria (CTC) were used. The two-drug combination was more myelosuppressive with 4 (1.5%) possibly treatment-related deaths, including 3 resulting from myelosuppression with infection and one case of renal failure associated with parotitis and infection. No deaths due to treatment were reported on the cisplatin arm. Nine cases of febrile neutropenia were reported on the combination therapy arm compared to 2 on the cisplatin arm. More patients required RBC and platelet transfusions on the gemtacin plus cisplatin arm.

Myelosuppression occurred more frequently on the combination arm, and in 4 possibly treatment-related deaths myelosuppression was observed. Sepsis was reported in 4% of patients on the gemtacin plus cisplatin arm compared to 1% on the cisplatin arm. Platelet transfusions were required in 21% of patients on the combination arm and 4% of patients on the cisplatin arm. Hemorrhagic events occurred in 14% of patients on the combination arm and 4% on the cisplatin arm. However, severe hemorrhagic events were rare. Red blood cell transfusions

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Gemcitabine exhibits cell phase specificity, primarily killing cells undergoing DNA synthesis (S-phase) and also blocking the progression of cells through the G1/S-phase boundary. Gemcitabine is metabolized intracellularly by nucleoside kinases to the active diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides. The cytotoxic effect of gemcitabine is attributed to a combination of two actions of the diphosphate and the triphosphate nucleosides, which leads to inhibition of DNA synthesis. First, gemcitabine diphosphate inhibits ribonucleotide reductase, which is responsible for catalyzing the reactions that generate the deoxyribonucleoside triphosphates for DNA synthesis. Inhibition of this enzyme by the diphosphate nucleoside causes a reduction in the concentrations of deoxyribonucleosides, including dCTP. Second, gemcitabine triphosphate competes with dCTP for incorporation into DNA. The reduction in the intracellular concentration of dCTP (by the action of the diphosphate) enhances the incorporation of gemcitabine triphosphate into DNA (see potential). After the gemcitabine nucleoside is incorporated into DNA, only one additional nucleotide is added to the growing DNA strand. After this addition, there is inhibition of further DNA synthesis. DNA polymerase activity is unable to remove the gemcitabine nucleotide and repair the growing DNA strands (masked chain termination). In CEM T lymphoblastoid cells, gemcitabine induces intermolecular DNA fragmentation, one of the characteristics of programmed cell death.

12.2 Pharmacodynamics

Gemcitabine demonstrated dose-dependent synergistic activity with cisplatin *in vitro*. No effect of cisplatin on gemcitabine triphosphate accumulation or DNA double-strand breaks was observed. *In vivo*, gemcitabine showed activity in combination with cisplatin against the LX1 and CALU-6 human lung xenografts, but human lung xenografts, including the H460 or H460 xenografts. Gemcitabine was synergistic with cisplatin in the Lewis lung murine xenograft. Sequential exposure to gemcitabine 4 hours before cisplatin produced the greatest interaction.

12.3 Pharmacokinetics

Absorption and Distribution
The pharmacokinetics of gemcitabine were examined in 353 patients, with various solid tumors. Pharmacokinetic parameters were derived using data from patients treated for varying durations of therapy given weekly with periodic rest weeks and using both short infusions (<70 minutes) and long infusions (70 to 285 minutes). The total gemcitabine dose varied from 500 to 3600 mg/m². The volume of distribution was increased with infusion length. Volume of distribution of gemcitabine was 50 L/m² following infusions lasting <70 minutes. For long infusions, the volume of distribution rose to 370 L/m². Gemcitabine pharmacokinetics are linear and are described by a 2-compartment model. Population pharmacokinetic analyses of combined single and multiple dose studies showed that the volume of distribution of gemcitabine was significantly influenced by duration of infusion and gender. Gemcitabine plasma protein binding is negligible. Metabolism

Gemcitabine disposition was studied in 5 patients who received a single 1000 mg/m²/30 minute infusion of radiolabeled drug. Within one (1) week, 92% to 98% of the dose was recovered, almost entirely in the urine. Gemcitabine (<10%) and the inactive uracil metabolite, 2'-deoxy-2'-difluorouridine (dFdU), accounted for 99% of the excreted dose. The metabolite dFdU is also found in plasma. The active metabolite, gemcitabine triphosphate, can be extracted from peripheral blood mononuclear cells. The half-life of the terminal phase for gemcitabine triphosphate from mononuclear cells ranges from 1.7 to 19.4 hours.

Excretion

Clearance of gemcitabine was affected by age and gender. The lower clearance in women and the elderly results in higher concentrations of gemcitabine for any given dose. Differences in either clearance or volume of distribution based on patient characteristics or the duration of infusion result in changes in half-life and plasma concentrations. Table 9 shows plasma clearance and half-life of gemcitabine following short infusions for typical patients by age and gender.

Table 9: Gemcitabine Clearance and Half-Life for the "Typical" Patient

Age	Clearance		Half-Life	
	Men (L/hr/m ²)	Women (L/hr/m ²)	Men (min)	Women (min)
29	92.2	69.4	42	49
45	75.7	57.0	48	57
65	55.1	41.5	61	73
79	40.7	30.7	79	94

* Half-life for patients receiving a short infusion (<70 min). Gemcitabine half-life for short infusions ranged from 42 to 94 minutes, and the value for long infusions varied from 245 to 288 minutes, depending on age and gender, reflecting a greatly increased volume of distribution with longer infusions.

Drug Interactions

When gemcitabine (1250 mg/m² on Days 1 and 8) and cisplatin (75 mg/m² on Day 1) were administered in NSCLC patients, the clearance of gemcitabine on Day 1 was 128 L/hr/m² and on Day 8 was 107 L/hr/m². The clearance of cisplatin in the same study was reported to be 9.94 mL/min/m² with a corresponding half-life of 134 hours (see Drug Interactions (7)). Analysis of data from metastatic breast cancer patients shows that, on average, gemcitabine has little or no effect on the pharmacokinetics (clearance and half-life) of paclitaxel and paclitaxel has little or no effect on the pharmacokinetics of gemcitabine. Data from NSCLC patients demonstrate that gemcitabine and carboplatin given in combination does not alter the pharmacokinetics of gemcitabine or carboplatin compared to administration of either single-agent. However, due to wide confidence intervals and small sample size, interpatient variability may be observed.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies to evaluate the carcinogenic potential of gemcitabine have not been conducted. Gemcitabine induced forward mutations *in vitro* in a mouse lymphoma (LS1787) assay and was clastogenic in an *in vivo* mouse micronucleus assay. Gemcitabine was negative when tested using the Ames, *in vivo* sister chromatid exchange, and *in vitro* chromosomal aberration assays, and did not cause unscheduled DNA synthesis *in vitro*. Gemcitabine IP doses of 0.5 mg/kg/day (about 1/700 the human dose on a mg/m² basis) in male mice had an effect on fertility with moderate to severe hypospERMATOSIS, decreased fertility, and decreased implantations. In female mice, fertility was not affected but maternal toxicities were observed at 1.5 mg/kg/day IV (about 1/200 the human dose on a mg/m² basis) and fetotoxicity or embryolethality was observed at 0.25 mg/kg/day IV (about 1/1300 the human dose on a mg/m² basis).

14 CLINICAL STUDIES

14.1 Ovarian Cancer

Gemcitabine was studied in a randomized Phase 3 study of 356 patients with advanced ovarian cancer that had relapsed at least 6 months after first-line platinum-based therapy. Patients were randomized to receive either gemcitabine 1000 mg/m² on Days 1 and 8 of a 21-day cycle and carboplatin AUC 4 administered after gemcitabine on Day 1 of each cycle or single-agent carboplatin AUC 5 administered on Day 1 of each 21-day cycle as the control arm. The primary endpoint of this study was progression free survival (PFS). Patient characteristics are shown in Table 10. The addition of gemcitabine to carboplatin resulted in statistically significant improvement in PFS and overall response rate as shown in Table 11 and Figure 1. Approximately 75% of patients in each arm received poststudy chemotherapy. Only 13 of 120 patients with documented poststudy chemotherapy regimen in the carboplatin arm received gemcitabine after progression. There was not a significant difference in overall survival between arms.

Table 10: Gemcitabine Plus Carboplatin Versus Carboplatin in Ovarian Cancer - Baseline Demographics and Clinical Characteristics

	Gemcitabine/Carboplatin	Carboplatin
Number of randomized patients	178	178
Median age, years	59	58
Range	36 to 78	21 to 81
Baseline ECOG performance status 0-1 ^a	94%	95%
Disease Status		
Evaluable	7.9%	2.8%
Dimensionally measurable	91.6%	95.5%
Platinum-free interval ^b		
6-12 months	39.9%	39.9%
>12 months	59.0%	59.0%
First-line therapy		
Platinum-taxane combination	70.2%	71.3%
Platinum-non-taxane combination	28.7%	27.5%
Platinum monotherapy	1.1%	1.1%

^a Nine patients (5 on the Gemcitabine plus carboplatin arm and 4 on the carboplatin arm) did not have baseline Eastern Cooperative Oncology Group (ECOG) performance status recorded.

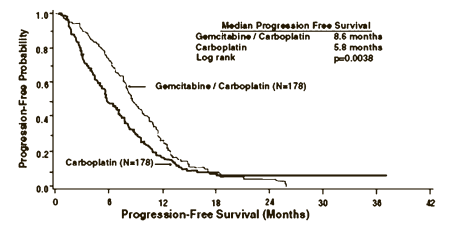
^b Three patients (2 on the Gemcitabine plus carboplatin arm and 1 on the carboplatin arm) had a platinum-free interval of less than 6 months.

Table 11: Gemcitabine Plus Carboplatin Versus Carboplatin in Ovarian Cancer - Results of Efficacy Analysis

	Gemcitabine/Carboplatin (N=178)	Carboplatin (N=178)	
PFS			
Median (95% C.I.) months	8.6 (8.0, 9.7)	5.8 (5.2, 7.1)	p=0.0038 ^a
Hazard Ratio (95% C.I.)		0.72 (0.57, 0.90)	
Overall Survival			
Median (95% C.I.) months	18.0 (16.2, 20.3)	17.3 (15.2, 19.3)	p=0.897 ^a
Hazard Ratio (95% C.I.)		0.98 (0.78, 1.24)	
Adjusted ^b Hazard Ratio (95% C.I.)		0.86 (0.67, 1.10)	
Investigator Reviewed Overall Response Rate ^c	47.2%	30.9%	p=0.0016 ^d
CR	14.6%	8.2%	
PR+PRIM ^e	32.6%	24.7%	
Independently Reviewed Overall Response Rate ^f	46.3%	35.6%	p=0.11 ^g
CR	9.1%	4.0%	
PR+PRIM	37.2%	31.7%	

^a Treatment adjusted for performance status, tumor area, and platinum-free interval.
^b Partial response non-measurable disease.
^c Independent reviewers could not evaluate disease demonstrated by sonography or physical exam.
^d Log Rank, unadjusted.
^e CR: Complete Response; PR: Partial Response; PRIM: Primary Response.
^f Independently reviewed cohort - Gemcitabine/Carboplatin N=121, Carboplatin N=101

Figure 1: Kaplan-Meier Curve of Progression Free Survival in Gemcitabine Plus Carboplatin Versus Carboplatin in Ovarian Cancer (N=356)



14.2 Breast Cancer

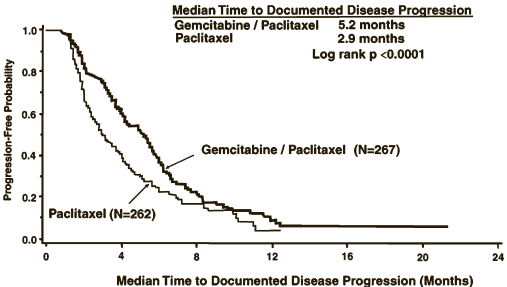
Data from a multi-national, randomized Phase 3 study (529 patients) support the use of gemcitabine in combination with paclitaxel for treatment of breast cancer patients who have received prior adjuvant/inadjuvant anthracycline chemotherapy unless clinically contraindicated. Gemcitabine 1250 mg/m² was administered on Days 1 and 8 of a 21-day cycle with paclitaxel 175 mg/m² administered prior to gemcitabine on Day 1 of each cycle. Single-agent paclitaxel 175 mg/m² was administered on Day 1 of each 21-day cycle as the control arm.

The addition of gemcitabine to paclitaxel resulted in statistically significant improvement in time to documented disease progression and overall response rate compared to monotherapy with paclitaxel as shown in Table 12 and Figure 2. Final survival analysis results at 440 events were Hazard Ratio of 0.86 (95% CI: 0.71 - 1.04) for the ITT population, as shown in Table 12.

	Gemcitabine/ Paclitaxel	Paclitaxel
Number of patients	267	262
Median age, years	53	52
Range	26 to 83	26 to 75
Metastatic disease	97.0%	96.9%
Baseline KPS ^a ≥ 90	70.4%	74.4%
Number of tumor sites		
1-2	56.6%	58.8%
>3	43.4%	41.2%
Visceral disease	73.4%	72.9%
Prior anthracycline	96.6%	95.8%
Overall Survival ^b		
Median (95% CI)	18.6 (16.5, 20.7)	15.8 (14.1, 17.3)
Hazard Ratio (95% CI)		0.86 (0.71, 1.04)
Time to Documented Disease Progression ^c		
Median (95% C.I.) months	5.2 (4.2, 5.6)	2.9 (2.6, 3.7)
Hazard Ratio (95% C.I.)		0.650 (0.524, 0.805)
Overall Response Rate ^d (95% C.I.)	40.8% (34.9, 46.7)	22.1% (17.1, 27.2)

^a Karnofsky Performance Status.
^b Based on the ITT population.
^c These represent reconciliation of investigator and Independent Review Committee assessments according to a predefined algorithm.

Figure 2: Kaplan-Meier Curve of Time to Documented Disease Progression in Gemcitabine Plus Paclitaxel Versus Paclitaxel Breast Cancer Study (N=529)



14.3 Non-Small Cell Lung Cancer (NSCLC)

Data from 2 randomized clinical studies (657 patients) support the use of gemcitabine in combination with cisplatin for the first-line treatment of patients with locally advanced or metastatic NSCLC. Gemcitabine plus cisplatin versus cisplatin: This study was conducted in Europe, the US, and Canada in 522 patients with inoperable Stage IIIA, IIIB, or IV NSCLC who had not received prior chemotherapy. Gemcitabine 1000 mg/m² was administered on Days 1, 8, and 15 of a 28-day cycle with cisplatin 100 mg/m² administered on Day 1 of each cycle. Single-agent cisplatin 100 mg/m² was administered on Day 1 of each 28-day cycle. The primary endpoint was survival. Patient demographics are shown in Table 13. An imbalance with regard to histology was observed with 48% of patients on the cisplatin arm and 37% of patients on the gemcitabine plus cisplatin arm having adenocarcinoma. The Kaplan-Meier survival curve is shown in Figure 3. Median survival time on the gemcitabine plus cisplatin arm was 8.0 months compared to 7.6 months on the single-agent cisplatin arm (Log rank p=0.008, two-sided). Median time to disease progression was 5.2 months on the gemcitabine plus cisplatin arm compared to 3.7 months on the cisplatin arm (Log rank p=0.002, two-sided). The objective response rate on the gemcitabine plus cisplatin arm was 26% compared to 10% with cisplatin (Fisher's Exact p<0.0001, two-sided). No difference between treatment arms with regard to duration of response was observed.

Gemcitabine plus cisplatin versus etoposide plus cisplatin: A second, multicenter, study in Stage IIIB or IV NSCLC randomized 135 patients to gemcitabine 1250 mg/m² on Days 1 and 8, and cisplatin 100 mg/m² on Day 1 of a 21-day cycle or to etoposide 100 mg/m² IV on Days 1, 2, and 3 and cisplatin 100 mg/m² on Day 1 of a 21-day cycle (Table 13). There was no significant difference in survival between the two treatment arms (Log rank p=0.18, two-sided). The median survival was 8.7 months for the gemcitabine plus cisplatin arm versus 7.8 months for the etoposide plus cisplatin arm. Median time to disease progression for the gemcitabine plus cisplatin arm was 5.0 months compared to 4.1 months on the etoposide plus cisplatin arm (Log rank p=0.015, two-sided). The objective response rate for the gemcitabine plus cisplatin arm was 33% compared to 14% on the etoposide plus cisplatin arm (Fisher's Exact p=0.01, two-sided).

Quality of Life (QOL): QOL was a secondary endpoint in both randomized studies. In the gemcitabine plus cisplatin versus cisplatin study, QOL was measured using the FACT-L, which assessed physical, social, emotional and functional well-being, and lung cancer symptoms. In the study of gemcitabine plus cisplatin versus etoposide plus cisplatin, QOL was measured using the EORTC QLQ-C30 and LC13, which assessed physical and psychological functioning and symptoms related to both lung cancer and its treatment. In both studies no significant differences were observed in QOL between the gemcitabine plus cisplatin arm and the comparator arm.

Figure 3: Kaplan-Meier Survival Curve in Gemcitabine Plus Cisplatin Versus Cisplatin NSCLC Study (N=522)

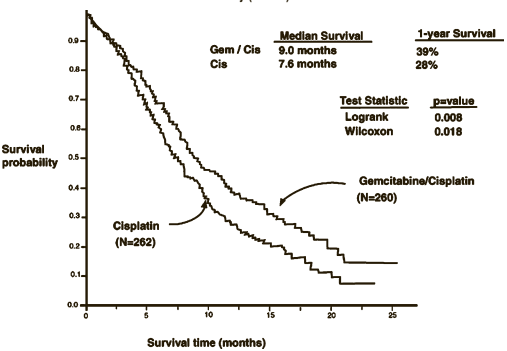


Table 13: Randomized Trials of Combination Therapy With Gemcitabine Plus Cisplatin in NSCLC

Trial	28-day Schedule ^a		28-day Schedule ^b			
	Gemcitabine/ Cisplatin	Cisplatin	Gemcitabine/ Cisplatin	Cisplatin		
Number of patients	260	262	69	66		
Male	182	186	64	61		
Female	78	76	5	5		
Median age, years	62	63	58	60		
Range	36 to 88	35 to 79	33 to 76	35 to 75		
Stage IIIA	7%	7%	N/A ^c	N/A ^c		
Stage IIIB	26%	23%	48%	52%		
Stage IV	67%	70%	52%	49%		
Baseline KPS ^d 70 to 80	41%	44%	45%	52%		
Baseline KPS ^d 90 to 100	57%	55%	55%	49%		
Survival						
Median, months	9.0	7.6	8.7	7.0		
(95% C.I.) months	8.2, 11.0	6.6, 8.8	7.8, 10.1	6.0, 9.7		
P-value		P=0.008		P=0.18		
Time to Disease Progression						
Median, months	5.2	3.7	5.0	4.1		
(95% C.I.) months	4.2, 5.7	3.0, 4.3	4.2, 6.4	2.4, 5.4		
P-value		P=0.009		P=0.015		
Tumor Response	26%	10%	P<0.0001 ^e	33%	14%	P=0.01 ^f

^a 28-day schedule — Gemcitabine plus cisplatin: Gemcitabine 1000 mg/m² on Days 1, 8, and 15 and cisplatin 100 mg/m² on Day 1 every 28 days; Single-agent cisplatin: cisplatin 100 mg/m² on Day 1 every 28 days.
^b 21-day schedule — Gemcitabine plus cisplatin: Gemcitabine 1250 mg/m² on Days 1 and 8 and cisplatin 100 mg/m² on Day 1 every 21 days; Etoposide plus Cisplatin: cisplatin 100 mg/m² on Day 1 and IV etoposide 100 mg/m² on Days 1, 2, and 3 every 21 days.
^c N/A - Not applicable.
^d Karnofsky Performance Status.
^e p-value for tumor response was calculated using the two-sided Fisher's Exact test for difference in binomial proportions. All other p-values were calculated using the Log rank test for difference in overall time to an event.

14.4 Pancreatic Cancer

Data from 2 clinical trials evaluated the use of gemcitabine in patients with locally advanced or metastatic pancreatic cancer. The first trial compared gemcitabine to 5-Fluorouracil (5-FU) in patients who had received no prior chemotherapy. A second trial studied the use of gemcitabine in pancreatic cancer patients previously treated with 5-FU or a 5-FU-containing regimen. In both studies, the first cycle of gemcitabine was administered intravenously at a dose of 1000 mg/m² over 30 minutes once weekly for up to 7 weeks (or until toxicity necessitated holding a dose) followed by a week of rest from treatment with gemcitabine. Subsequent cycles consisted of injections once weekly for 3 consecutive weeks out of every 4 weeks. The primary efficacy parameter in these studies was "clinical benefit response," which is a measure of clinical improvement based on analgesic consumption, pain intensity, performance status, and weight change. Definitions for improvement in these variables were formulated prospectively during the design of the 2 trials. A patient was considered a clinical benefit responder if either:
i) the patient showed a ≥50% reduction in pain intensity (Memorial Pain Assessment Cart) or analgesic consumption, or a ≥2-point or greater improvement in performance status (Karnofsky Performance Status) for a period of at least 4 consecutive weeks, without showing any sustained worsening in any of the other parameters. Sustained worsening was defined as 4 consecutive weeks with either any increase in pain intensity or analgesic consumption or a ≥2-point decrease in performance status occurring during the first 12 weeks of therapy.

OR:
ii) the patient was stable on all of the aforementioned parameters, and showed a marked, sustained weight gain (≥7% increase maintained for ≥4 weeks) not due to fluid accumulation.

The first study was a multicenter (17 sites in US and Canada), prospective, single-blind, two-arm, randomized, comparison of gemcitabine and 5-FU in patients with locally advanced or metastatic pancreatic cancer who had received no prior treatment with chemotherapy. 5-FU was administered intravenously at a weekly dose of 600 mg/m² for 30 minutes. The results from this randomized trial are shown in Table 14. Patients treated with gemcitabine had statistically significant increases in clinical benefit response, survival, and time to disease progression compared to 5-FU. The Kaplan-Meier curve for survival is shown in Figure 4. No confirmed objective tumor responses were observed with either treatment.

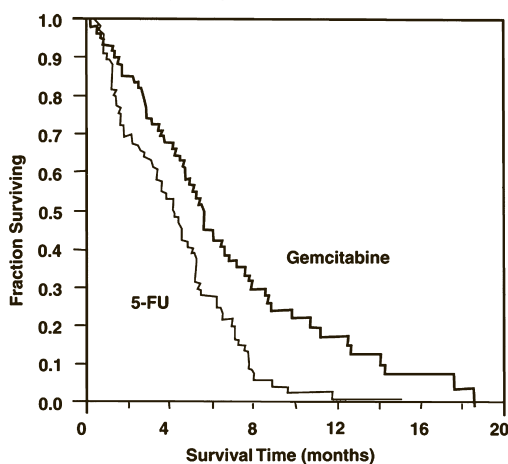
Table 14: Gemcitabine Versus 5-FU in Pancreatic Cancer

	Gemcitabine	5-FU	
Number of patients	63	63	
Male	34	34	
Female	29	29	
Median age	62 years	61 years	
Range	37 to 79	36 to 77	
Stage IV disease	71.4%	76.2%	
Baseline KPS ^a < 70	69.8%	68.3%	
Clinical benefit response	22.2% (N=14)	4.8% (N=3)	p<0.004 ^b
Survival			p=0.0009
Median	5.7 months	4.2 months	
6-month probability ^c	(N=30) 46%	(N=19) 29%	
9-month probability ^c	(N=14) 24%	(N=4) 5%	
1-year probability ^c	(N=9) 18%	(N=2) 2%	
Range	0.2 to 18.6 months	0.4 to 15.1+ months	
95% C.I. of the median	4.7 to 6.9 months	3.1 to 5.1 months	
Time to Disease Progression			p=0.0013
Median	2.1 months	0.9 months	
Range	0.1+ to 9.4 months	0.1 to 12.0+ months	
95% C.I. of the median	1.9 to 3.4 months	0.9 to 1.1 months	

^a Karnofsky Performance Status.
^b Kaplan-Meier estimates.
^c N=number of patients.
^d No progression at last visit; remains alive.
^e The p-value for clinical benefit response was calculated using the two-sided test for difference in binomial proportions. All other p-values were calculated using the Log rank test for difference in overall time to an event.

Clinical benefit response was achieved by 14 patients treated with gemcitabine and 3 patients treated with 5-FU. One patient on the gemcitabine arm showed improvement in all 3 primary parameters (pain intensity, analgesic consumption, and performance status). Eleven patients on the gemcitabine arm and 2 patients on the 5-FU arm showed improvement in analgesic consumption and/or pain intensity with stable performance status. Two patients on the gemcitabine arm showed improvement in analgesic consumption or pain intensity with improvement in performance status. One patient on the 5-FU arm was stable with regard to pain intensity and analgesic consumption with improvement in performance status. No patient on either arm achieved a clinical benefit response based on weight gain.

Figure 4: Kaplan-Meier Survival Curve



The second trial was a multicenter (17 US and Canadian centers), open-label study of gemcitabine in 63 patients with advanced pancreatic cancer previously treated with 5-FU or a 5-FU-containing regimen. The study showed a clinical benefit response rate of 27% and median survival of 3.9 months.

14.5 Other Clinical Studies

When gemcitabine was administered more frequently than once weekly or with infusions longer than 60 minutes, increased toxicity was observed. Results of a Phase 1 study of gemcitabine to assess the maximum tolerated dose (MTD) on a daily x 5 schedule showed that patients developed significant hypotension and severe flu-like symptoms that were intolerable at doses above 10 mg/m². The incidence and severity of these events were dose-related. Other Phase 1 studies using a twice-weekly schedule reached MTDs of only 65 mg/m² (30-minute infusion) and 150 mg/m² (5-minute bolus). The dose-limiting toxicities were thrombocytopenia and flu-like symptoms, particularly asthma. In a Phase 1 study to assess the maximum tolerated infusion time, clinically significant toxicity, defined as myelodepression, was seen with weekly doses of 300 mg/m² at or above a 270-minute infusion time. The half-life of gemcitabine is influenced by the length of the infusion (see Clinical Pharmacology (12.3)) and the toxicity appears to be increased if gemcitabine is administered more frequently than once weekly or with infusions longer than 60 minutes (see Warnings and Precautions (3.1)).

15 REFERENCES

1. NIOSH Alert: Preventing occupational exposures to antineoplastic and other hazardous drugs in healthcare settings. 2004. U.S. Department of Health and Human Services, Public Health Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health. DHHS (NIOSH) Publication No. 2004-165.
2. OSHA Technical Manual, TED 1-1-15A, Section VI, Chapter 2, Controlling Occupational Exposure to Hazardous Drugs, OSHA, 1999. http://www.osha-slc.gov/dts/osta/vtom/vtom_v1_2.html
3. American Society of Health-System Pharmacists. ASPH Guidelines on Handling Hazardous Drugs. Am J Health-Syst Pharm. 2006;63: 1172-1193.
4. Pudovitch, M., White, J. M., & Kelleher, L. O. (eds.) 2005. Chemotherapy and Biotherapy Guidelines and Recommendations for Practice (2nd ed.). Pittsburgh, PA: Oncology Nursing Society.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Gemcitabine for Injection, USP is available in sterile single-use vials individually packaged in a carton containing:
2 g white to off-white, lyophilized powder in a 100-mL size sterile single-use vial- NDC 0409-0187-01

16.2 Storage and Handling

Unopened vials of Gemcitabine for Injection, USP are stable until the expiration date indicated on the package when stored at controlled room temperature 20° to 25°C (68° to 77°F) and that allows for excursions between 15° to 30°C (59° to 86°F) (See USP Controlled Room Temperature). (see Dosage and Administration (2.5 and 2.6))

17 PATIENT COUNSELING INFORMATION

17.1 Low Blood Cell Counts

Patients should be adequately informed of the risk of low blood cell counts and instructed to immediately contact their physician should any sign of infection develop including fever. Patients should also contact their physician if bleeding or symptoms of anemia occur. (see Warnings and Precautions (3.2))

17.2 Pregnancy

There are no adequate and well-controlled studies of gemcitabine in pregnant women. Based on animal studies gemcitabine can cause fetal harm when administered to a pregnant woman. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the risks to the fetus need to be discussed with their physician. (see Warnings and Precautions (5.6