

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use GEMZAR safely and effectively. See full prescribing information for GEMZAR.

GEMZAR (gemcitabine hydrochloride) Injection, Powder, Lyophilized, For Solution For Intravenous Use

Initial U.S. Approval: 1996

-----**INDICATIONS AND USAGE**-----

Gemzar® is a nucleoside metabolic inhibitor indicated for:

- 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)

-----**DOSAGE AND ADMINISTRATION**-----

Gemzar 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 from 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)

-----**DOSAGE FORMS AND STRENGTHS**-----

- 200 mg vial for injection (3)
- 1 g vial for injection (3)

-----**CONTRAINDICATIONS**-----

Patients with a known hypersensitivity to Gemcitabine (4)

-----**WARNINGS AND PRECAUTIONS**-----

- Infusion time and dose frequency: Increased toxicity with infusion time >60 minutes or dosing more frequently than once weekly. (5.1)
- Hematology: Monitor for myelosuppression, which can be dose-limiting. (5.2, 5.7)
- Pulmonary toxicity: Discontinue Gemzar 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 Gemzar 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 Gemzar 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, proteinuria, fever, hematuria, rash, thrombocytopenia, dyspnea (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Eli Lilly and Company at 1-800-LillyRx (1-800-545 5979) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION

Revised:MM/YYYY

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Ovarian Cancer

Gemzar 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

Gemzar 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

Gemzar 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

Gemzar 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. Gemzar is indicated for patients previously treated with 5-FU.

2 DOSAGE AND ADMINISTRATION

Gemzar is for intravenous use only. Gemzar may be administered on an outpatient basis.

2.1 Ovarian Cancer

Gemzar 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 Gemzar administration. Patients should be monitored prior to each dose with a complete blood count, including differential counts. Patients should have an absolute granulocyte count $\geq 1500 \times 10^6/L$ and a platelet count $\geq 100,000 \times 10^6/L$ prior to each cycle.

Dose Modifications

Gemzar dosage adjustments for hematological toxicity within a cycle of treatment is based on the granulocyte and platelet counts taken on Day 8 of therapy. If marrow suppression is detected, Gemzar dosage should be modified according to guidelines in Table 1.

Table 1: Day 8 Dosage Reduction Guidelines for Gemzar in Combination with Carboplatin

Absolute granulocyte count ($\times 10^6/L$)		Platelet count ($\times 10^6/L$)	% 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 Gemzar should be held or decreased by 50% depending on the judgment of the treating physician. For carboplatin dosage adjustment, see manufacturer's prescribing information.

Dose adjustment for Gemzar in combination with carboplatin for subsequent cycles is based upon observed toxicity. The dose of Gemzar 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 $< 500 \times 10^6/L$ for more than 5 days
- Absolute granulocyte count $< 100 \times 10^6/L$ for more than 3 days
- Febrile neutropenia
- Platelets $< 25,000 \times 10^6/L$
- Cycle delay of more than one week due to toxicity

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

2.2 Breast Cancer

Gemzar 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 Gemzar administration. Patients should be monitored prior to each dose with a complete blood count, including differential counts. Patients should have an absolute granulocyte count $\geq 1500 \times 10^6/L$ and a platelet count $\geq 100,000 \times 10^6/L$ prior to each cycle.

Dose Modifications

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

Table 2: Day 8 Dosage Reduction Guidelines for Gemzar in Combination with Paclitaxel

Absolute granulocyte count (x 10 ⁶ /L)		Platelet count (x 10 ⁶ /L)	% of full dose
≥1200	and	>75,000	100
1000-1199	or	50,000-75,000	75
700-999	and	≥50,000	50
<700	or	<50,000	Hold

In general, for severe (Grade 3 or 4) non-hematological toxicity, except alopecia and nausea/vomiting, therapy with Gemzar 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 (14.3)*]. With the 4-week schedule, Gemzar 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 Gemzar. With the 3-week schedule, Gemzar 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 Gemzar on Day 1. See prescribing information for cisplatin administration and hydration guidelines.

Dose Modifications

Dosage adjustments for hematologic toxicity may be required for Gemzar and for cisplatin. Gemzar dosage adjustment for hematological toxicity is based on the granulocyte and platelet counts taken on the day of therapy. Patients receiving Gemzar 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 Gemzar 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 (Grade 3/4 serum creatinine toxicity for Gemzar plus cisplatin was 5% versus 2% for cisplatin alone).

2.4 Pancreatic Cancer

Gemzar 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 were somewhat less able to progress to subsequent cycles [see *Warnings and Precautions (5.2)* and *Clinical Pharmacology (12.3)*].

Patients receiving Gemzar 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: Dosage Reduction Guidelines

Absolute granulocyte count (x 10 ⁶ /L)		Platelet count (x 10 ⁶ /L)	% of full dose
≥1000	and	≥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. Gemzar 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 Gemzar who complete 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 x 10⁶/L and 100,000 x 10⁶/L, respectively, and if non-hematologic toxicity has not been greater than WHO Grade 1. If patients tolerate the subsequent course of Gemzar at the increased dose, the dose for the next cycle can be further increased by 20%, provided again that the AGC and platelet nadirs exceed 1500 x 10⁶/L and 100,000 x 10⁶/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 Gemzar solutions. The use of gloves is recommended. If Gemzar 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 animal studies, 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 (15)*].

2.6 Preparation for Intravenous Infusion Administration

The recommended diluent for reconstitution of Gemzar is 0.9% Sodium Chloride Injection without preservatives. Due to solubility considerations, the maximum concentration for Gemzar upon reconstitution is 40 mg/mL. Reconstitution at concentrations greater than 40 mg/mL may result in incomplete dissolution, and should be avoided.

To reconstitute, add 5 mL of 0.9% Sodium Chloride Injection to the 200-mg vial or 25 mL of 0.9% Sodium Chloride Injection to the 1-g vial. Shake to dissolve. These dilutions each yield a gemcitabine concentration of 38 mg/mL which includes accounting for the displacement volume of the lyophilized powder (0.26 mL for the 200-mg vial or 1.3 mL for the 1-g vial). The total volume upon reconstitution will be 5.26 mL or 26.3 mL, respectively. Complete withdrawal of the vial contents will provide 200 mg or 1 g of gemcitabine, 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 Gemzar is a clear, 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, Gemzar 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 Gemzar should not be refrigerated, as crystallization may occur.

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

3 DOSAGE FORMS AND STRENGTHS

GEMZAR (gemcitabine for injection, USP) is a white to off-white lyophilized powder available in sterile single-use vials containing 200 mg or 1 g gemcitabine.

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

Patients receiving therapy with Gemzar 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

Gemzar 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 Gemzar. In cases of severe lung toxicity, Gemzar 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 Gemzar. 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)*].

Gemzar 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 (8.6)*]

5.5 Hepatic

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

Gemzar 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 Gemzar 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)*]

ALT	68	8	2	72	10	1	
AST	67	6	2	78	12	5	
Alkaline Phosphatase	55	7	2	77	16	4	
Bilirubin	13	2	<1	26	6	2	
Renal							<1
Proteinuria	45	<1	0	32	<1	0	
Hematuria	35	<1	0	23	0	0	
BUN	16	0	0	15	0	0	
Creatinine	8	<1	0	6	0	0	
Non-laboratory^f							
Nausea and Vomiting	69	13	1	71	10	2	<1
Fever	41	2	0	38	2	0	<1
Rash	30	<1	0	28	<1	0	<1
Dyspnea	23	3	<1	10	0	<1	<1
Diarrhea	19	1	0	30	3	0	0
Hemorrhage	17	<1	<1	4	2	<1	<1
Infection	16	1	<1	10	2	<1	<1
Alopecia	15	<1	0	16	0	0	0
Stomatitis	11	<1	0	10	<1	0	<1
Somnolence	11	<1	<1	11	2	<1	<1
Paresthesias	10	<1	0	10	<1	0	0

^a Grade based on criteria from the World Health Organization (WHO).

^b N=699-974; all patients with laboratory or non-laboratory data.

^c N=161-241; all pancreatic cancer patients with laboratory or non-laboratory data.

^d N=979.

^e Regardless of causality.

^f Table includes non-laboratory data with incidence for all patients $\geq 10\%$. For approximately 60% of the patients, non-laboratory adverse reactions were graded only if assessed to be possibly drug-related.

Hematologic — In studies in pancreatic cancer myelosuppression is the dose-limiting toxicity with Gemzar, but <1% of patients discontinued therapy for either anemia, leukopenia, or thrombocytopenia. Red blood cell transfusions were required by 19% of patients. The incidence of sepsis was less than 1%. Petechiae or mild blood loss (hemorrhage), from any cause, was reported in 16% of patients; less than 1% of patients required platelet transfusions. Patients should be monitored for myelosuppression during Gemzar therapy and dosage modified or suspended according to the degree of hematologic toxicity. [see *Dosage and Administration* (2.1, 2.2, 2.3, and 2.4)]

Gastrointestinal — Nausea and vomiting were commonly reported (69%) but were usually of mild to moderate severity. Severe nausea and vomiting (WHO Grade 3/4) occurred in <15% of patients. Diarrhea was reported by 19% of patients, and stomatitis by 11% of patients.

Hepatic — In clinical trials, Gemzar was associated with transient elevations of one or both serum transaminases in approximately 70% of patients, but there was no evidence of increasing hepatic toxicity with either longer duration of exposure to Gemzar or with greater total cumulative dose. Serious hepatotoxicity, including liver failure and death, has been reported very rarely in patients receiving Gemzar alone or in combination with other potentially hepatotoxic drugs. [see *Adverse Reactions* (6.2)]

Renal — In clinical trials, mild proteinuria and hematuria were commonly reported. Clinical findings consistent with the Hemolytic Uremic Syndrome (HUS) were reported in 6 of 2429 patients (0.25%) receiving Gemzar in clinical trials. Four patients developed HUS on Gemzar therapy, 2 immediately posttherapy. The diagnosis of HUS should be considered if the patient develops anemia with evidence of microangiopathic hemolysis, elevation of bilirubin or LDH, reticulocytosis, severe thrombocytopenia, and/or evidence of renal failure (elevation of serum creatinine or BUN). Gemzar therapy should be discontinued immediately. Renal failure may not be reversible even with discontinuation of therapy and dialysis may be required. [see *Adverse Reactions* (6.2)]

Fever — The overall incidence of fever was 41%. This is in contrast to the incidence of infection (16%) and indicates that Gemzar may cause fever in the absence of clinical infection. Fever was frequently associated with other flu-like symptoms and was usually mild and clinically manageable.

Rash — Rash was reported in 30% of patients. The rash was typically a macular or finely granular maculopapular pruritic eruption of mild to moderate severity involving the trunk and extremities. Pruritus was reported for 13% of patients.

Pulmonary — In clinical trials, dyspnea, unrelated to underlying disease, has been reported in association with Gemzar therapy. Dyspnea was occasionally accompanied by bronchospasm. Pulmonary toxicity has been reported with the use of Gemzar. [see *Adverse Reactions* (6.2)] The etiology of these effects is unknown. If such effects develop, Gemzar should be discontinued. Early use of supportive care measures may help ameliorate these conditions.

Edema — Edema (13%), peripheral edema (20%), and generalized edema (<1%) were reported. Less than 1% of patients discontinued due to edema.

Flu-like Symptoms — “Flu syndrome” was reported for 19% of patients. Individual symptoms of fever, asthenia, anorexia, headache, cough, chills, and myalgia were commonly reported. Fever and asthenia were also reported frequently as isolated symptoms. Insomnia, rhinitis, sweating, and malaise were reported infrequently. Less than 1% of patients discontinued due to flu-like symptoms.

Infection — Infections were reported for 16% of patients. Sepsis was rarely reported (<1%).

Alopecia — Hair loss, usually minimal, was reported by 15% of patients.

Neurotoxicity — There was a 10% incidence of mild paresthesias and a <1% rate of severe paresthesias.

Extravasation — Injection-site related events were reported for 4% of patients. There were no reports of injection site necrosis. Gemzar is not a vesicant.

Allergic — Bronchospasm was reported for less than 2% of patients. Anaphylactoid reaction has been reported rarely. Gemzar should not be administered to patients with a known hypersensitivity to this drug [see *Contraindications (4)*].

Cardiovascular — During clinical trials, 2% of patients discontinued therapy with Gemzar due to cardiovascular events such as myocardial infarction, cerebrovascular accident, arrhythmia, and hypertension. Many of these patients had a prior history of cardiovascular disease [see *Adverse Reactions (6.2)*].

Combination Use in Non-Small Cell Lung Cancer:

In the Gemzar plus cisplatin versus cisplatin study, dose adjustments occurred with 35% of Gemzar injections and 17% of cisplatin injections on the combination arm, versus 6% on the cisplatin-only arm. Dose adjustments were required in greater than 90% of patients on the combination, versus 16% on cisplatin. Study discontinuations for possibly drug-related adverse reactions occurred in 15% of patients on the combination arm and 8% of patients on the cisplatin arm. With a median of 4 cycles of Gemzar plus cisplatin treatment, 94 of 262 patients (36%) experienced a total of 149 hospitalizations due to possibly treatment-related adverse reactions. With a median of 2 cycles of cisplatin treatment, 61 of 260 patients (23%) experienced 78 hospitalizations due to possibly treatment-related adverse reactions.

In the Gemzar plus cisplatin versus etoposide plus cisplatin study, dose adjustments occurred with 20% of Gemzar injections and 16% of cisplatin injections in the Gemzar 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 Gemzar plus cisplatin treatment, 15 of 69 patients (22%) 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 Gemzar plus cisplatin patients, compared with 68% on the etoposide plus cisplatin arm. Study discontinuations for possibly drug-related adverse reactions occurred in 14% of patients on the Gemzar plus cisplatin arm and in 8% of patients on the etoposide plus cisplatin arm. The incidence of myelosuppression was increased in frequency with Gemzar plus cisplatin treatment (~90%) compared to that with the Gemzar monotherapy (~60%). With combination therapy Gemzar 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 Gemzar plus cisplatin versus cisplatin study in non-small cell lung 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 pancytopenia 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 Gemzar 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 Gemzar plus cisplatin arm compared to 1% on the cisplatin arm. Platelet transfusions were required in 21% of patients on the combination arm and <1% 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 were required in 39% of the patients on the Gemzar plus cisplatin arm, versus 13% on the cisplatin arm. The data suggest cumulative anemia with continued Gemzar plus cisplatin use.

Nausea and vomiting despite the use of antiemetics occurred more often with Gemzar plus cisplatin therapy (78%) than with cisplatin alone (71%). In studies with single-agent Gemzar, a lower incidence of nausea and vomiting (58% to 69%) was reported. Renal function abnormalities, hypomagnesemia, neuromotor, neurocortical, and neurocerebellar toxicity occurred more often with Gemzar plus cisplatin than with cisplatin monotherapy. Neurohearing toxicity was similar on both arms.

Cardiac dysrhythmias of Grade 3 or greater were reported in 7 (3%) patients treated with Gemzar plus cisplatin compared to one (<1%) Grade 3 dysrhythmia reported with cisplatin therapy. Hypomagnesemia and hypokalemia were associated with one Grade 4 arrhythmia on the Gemzar plus cisplatin combination arm.

Table 6 presents data from the randomized study of Gemzar plus cisplatin versus etoposide plus cisplatin in 135 patients with NSCLC. One death (1.5%) was reported on the Gemzar plus cisplatin arm due to febrile neutropenia associated with renal failure which was possibly treatment-related. No deaths related to treatment occurred on the etoposide plus cisplatin arm. The overall incidence of Grade 4 neutropenia on the Gemzar plus cisplatin arm was less than on the etoposide plus cisplatin arm (28% versus 56%). Sepsis was experienced by 2% of patients on both treatment arms. Grade 3 anemia and Grade 3/4 thrombocytopenia were more common on the Gemzar plus cisplatin arm. RBC transfusions were given to 29% of the patients who received Gemzar plus cisplatin versus 21% of patients who received etoposide plus cisplatin. Platelet transfusions were given to 3% of the patients who received Gemzar plus cisplatin versus 8% of patients who received etoposide plus cisplatin. Grade 3/4 nausea and

vomiting were also more common on the Gemzar plus cisplatin arm. On the Gemzar plus cisplatin arm, 7% of participants were hospitalized due to febrile neutropenia compared to 12% on the etoposide plus cisplatin arm. More than twice as many patients had dose reductions or omissions of a scheduled dose of Gemzar as compared to etoposide, which may explain the differences in the incidence of neutropenia and febrile neutropenia between treatment arms. Flu syndrome was reported by 3% of patients on the Gemzar plus cisplatin arm with none reported on the comparator arm. Eight patients (12%) on the Gemzar plus cisplatin arm reported edema compared to one patient (2%) on the etoposide plus cisplatin arm.

Table 5: Selected CTC-Graded Adverse Reactions From Comparative Trial of Gemzar Plus Cisplatin Versus Single-Agent Cisplatin in NSCLC

	CTC Grades (% incidence) ^a			CTC Grades (% incidence) ^a		
	Gemzar plus Cisplatin ^b			Cisplatin ^c		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Laboratory^d						
Hematologic						
Anemia	89	22	3	67	6	1
RBC Transfusion ^e	39			13		
Leukopenia	82	35	11	25	2	1
Neutropenia	79	22	35	20	3	1
Thrombocytopenia	85	25	25	13	3	1
Platelet Transfusions ^e	21			<1		
Lymphocytes	75	25	18	51	12	5
Hepatic						
Transaminase	22	2	1	10	1	0
Alkaline Phosphatase	19	1	0	13	0	0
Renal						
Proteinuria	23	0	0	18	0	0
Hematuria	15	0	0	13	0	0
Creatinine	38	4	<1	31	2	<1
Other Laboratory						
Hyperglycemia	30	4	0	23	3	0
Hypomagnesemia	30	4	3	17	2	0
Hypocalcemia	18	2	0	7	0	<1
Non-laboratory^f						
Nausea	93	25	2	87	20	<1
Vomiting	78	11	12	71	10	9
Alopecia	53	1	0	33	0	0
Neuro Motor	35	12	0	15	3	0
Neuro Hearing	25	6	0	21	6	0
Diarrhea	24	2	2	13	0	0
Neuro Sensory	23	1	0	18	1	0
Infection	18	3	2	12	1	0
Fever	16	0	0	5	0	0
Neuro Cortical	16	3	1	9	1	0
Neuro Mood	16	1	0	10	1	0
Local	15	0	0	6	0	0
Neuro Headache	14	0	0	7	0	0
Stomatitis	14	1	0	5	0	0
Hemorrhage	14	1	0	4	0	0
Dyspnea	12	4	3	11	3	2
Hypotension	12	1	0	7	1	0
Rash	11	0	0	3	0	0

^a Grade based on Common Toxicity Criteria (CTC). Table includes data for adverse reactions with incidence $\geq 10\%$ in either arm.

^b N=217-253; all Gemzar plus cisplatin patients with laboratory or non-laboratory data. Gemzar at 1000 mg/m² on Days 1, 8, and 15 and cisplatin at 100 mg/m² on Day 1 every 28 days.

^c N=213-248; all cisplatin patients with laboratory or non-laboratory data. Cisplatin at 100 mg/m² on Day 1 every 28 days.

^d Regardless of causality.

^e Percent of patients receiving transfusions. Percent transfusions are not CTC-graded events.

^f Non-laboratory events were graded only if assessed to be possibly drug-related.

Table 6: Selected WHO-Graded Adverse Reactions From Comparative Trial of Gemzar Plus Cisplatin Versus Etoposide Plus Cisplatin in NSCLC

	WHO Grades (% incidence) ^a					
	Gemzar plus Cisplatin ^b			Etoposide plus Cisplatin ^c		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Laboratory^d						
Hematologic						
Anemia	88	22	0	77	13	2
RBC Transfusions ^e	29			21		
Leukopenia	86	26	3	87	36	7
Neutropenia	88	36	28	87	20	56
Thrombocytopenia	81	39	16	45	8	5
Platelet Transfusions ^e	3			8		
Hepatic						
ALT	6	0	0	12	0	0
AST	3	0	0	11	0	0
Alkaline Phosphatase	16	0	0	11	0	0
Bilirubin	0	0	0	0	0	0
Renal						
Proteinuria	12	0	0	5	0	0
Hematuria	22	0	0	10	0	0
BUN	6	0	0	4	0	0
Creatinine	2	0	0	2	0	0
Non-laboratory^{f,g}						
Nausea and Vomiting	96	35	4	86	19	7
Fever	6	0	0	3	0	0
Rash	10	0	0	3	0	0
Dyspnea	1	0	1	3	0	0
Diarrhea	14	1	1	13	0	2
Hemorrhage	9	0	3	3	0	3
Infection	28	3	1	21	8	0
Alopecia	77	13	0	92	51	0
Stomatitis	20	4	0	18	2	0
Somnolence	3	0	0	3	2	0
Paresthesias	38	0	0	16	2	0

^a Grade based on criteria from the World Health Organization (WHO).

^b N=67-69; all Gemzar plus cisplatin patients with laboratory or non-laboratory data. Gemzar at 1250 mg/m² on Days 1 and 8 and cisplatin at 100 mg/m² on Day 1 every 21 days.

^c N=57-63; all cisplatin plus etoposide patients with laboratory or non-laboratory data. Cisplatin at 100 mg/m² on Day 1 and IV etoposide at 100 mg/m² on Days 1, 2, and 3 every 21 days.

^d Regardless of causality.

^e Percent of patients receiving transfusions. Percent transfusions are not WHO-graded events.

^f Non-laboratory events were graded only if assessed to be possibly drug-related.

^g Pain data were not collected.

Combination Use in Breast Cancer:

In the Gemzar plus paclitaxel versus paclitaxel study, dose reductions occurred with 8% of Gemzar injections and 5% of paclitaxel injections on the combination arm, versus 2% on the paclitaxel arm. On the combination arm, 7% of Gemzar doses were omitted and <1% of paclitaxel doses were omitted, compared to <1% of paclitaxel doses on the paclitaxel arm. A total of 18 patients (7%) on the Gemzar plus paclitaxel arm and 12 (5%) on the paclitaxel arm discontinued the study because of adverse reactions. There were two deaths on study or within 30 days after study drug discontinuation that were possibly drug-related, one on each arm.

Table 7 presents the safety data occurrences of ≥10% (all grades) from the Gemzar plus paclitaxel versus paclitaxel study in breast cancer.

Table 7: Adverse Reactions From Comparative Trial of Gemzar Plus Paclitaxel Versus Single-Agent Paclitaxel in Breast Cancer^a

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	Gemzar plus Paclitaxel (N=262)			Paclitaxel (N=259)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Laboratory^b						
Hematologic						
Anemia	69	6	1	51	3	<1
Neutropenia	69	31	17	31	4	7
Thrombocytopenia	26	5	<1	7	<1	<1
Leukopenia	21	10	1	12	2	0
Hepatobiliary						
ALT	18	5	<1	6	<1	0
AST	16	2	0	5	<1	0
Non-laboratory^c						
Alopecia	90	14	4	92	19	3
Neuropathy-sensory	64	5	<1	58	3	0
Nausea	50	1	0	31	2	0
Fatigue	40	6	<1	28	1	<1
Myalgia	33	4	0	33	3	<1
Vomiting	29	2	0	15	2	0
Arthralgia	24	3	0	22	2	<1
Diarrhea	20	3	0	13	2	0
Anorexia	17	0	0	12	<1	0
Neuropathy-motor	15	2	<1	10	<1	0
Stomatitis/pharyngitis	13	1	<1	8	<1	0
Fever	13	<1	0	3	0	0
Rash/desquamation	11	<1	<1	5	0	0

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^a Grade based on Common Toxicity Criteria (CTC) Version 2.0 (all grades \geq 10%).

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^b Regardless of causality.

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^c Non-laboratory events were graded only if assessed to be possibly drug-related.

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The following are the clinically relevant adverse reactions that occurred in $>$ 1% and $<$ 10% (all grades) of patients on either arm. In parentheses are the incidences of Grade 3 and 4 adverse reactions (Gemzar plus paclitaxel versus paclitaxel): febrile neutropenia (5.0% versus 1.2%), infection (0.8% versus 0.8%), dyspnea (1.9% versus 0), and allergic reaction/hypersensitivity (0 versus 0.8%).

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No differences in the incidence of laboratory and non-laboratory events were observed in patients 65 years or older, as compared to patients younger than 65.

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Combination Use in Ovarian Cancer:

In the Gemzar plus carboplatin versus carboplatin study, dose reductions occurred with 10.4% of Gemzar injections and 1.8% of carboplatin injections on the combination arm, versus 3.8% on the carboplatin alone arm. On the combination arm, 13.7% of Gemzar doses were omitted and 0.2% of carboplatin doses were omitted, compared to 0% of carboplatin doses on the carboplatin alone arm. There were no differences in discontinuations due to adverse reactions between arms (10.9% versus 9.8%, respectively).

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Table 8 presents the adverse reactions (all grades) occurring in \geq 10% of patients in the ovarian cancer study.

Table 8: Adverse Reactions From Comparative Trial of Gemzar Plus Carboplatin Versus Single-Agent Carboplatin in Ovarian Cancer^a

	Gemzar plus Carboplatin (N=175)			Carboplatin (N=174)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Laboratory^b						
Hematologic						
Neutropenia	90	42	29	58	11	1
Anemia	86	22	6	75	9	2
Leukopenia	86	48	5	70	6	<1
Thrombocytopenia	78	30	5	57	10	1
RBC Transfusions ^c	38			15		
Platelet Transfusions ^c	9			3		

Non-laboratory^b						
Nausea	69	6	0	61	3	0
Alopecia	49	0	0	17	0	0
Vomiting	46	6	0	36	2	<1
Constipation	42	6	1	37	3	0
Fatigue	40	3	<1	32	5	0
Neuropathy-sensory	29	1	0	27	2	0
Diarrhea	25	3	0	14	<1	0
Stomatitis/pharyngitis	22	<1	0	13	0	0
Anorexia	16	1	0	13	0	0

^a Grade based on Common Toxicity Criteria (CTC) Version 2.0 (all grades $\geq 10\%$).

^b Regardless of causality.

^c Percent of patients receiving transfusions. Transfusions are not CTC-graded events. Blood transfusions included both packed red blood cells and whole blood.

In addition to blood product transfusions as listed in Table 8, myelosuppression was also managed with hematopoietic agents. These agents were administered more frequently with combination therapy than with monotherapy (granulocyte growth factors: 23.6% and 10.1%, respectively; erythropoietic agents: 7.3% and 3.9%, respectively).

The following are the clinically relevant adverse reactions, regardless of causality, that occurred in $>1\%$ and $<10\%$ (all grades) of patients on either arm. In parentheses are the incidences of Grade 3 and 4 adverse reactions (Gemzar plus carboplatin versus carboplatin): AST or ALT elevation (0 versus 1.2%), dyspnea (3.4% versus 2.9%), febrile neutropenia (1.1% versus 0), hemorrhagic event (2.3% versus 1.1%), hypersensitivity reaction (2.3% versus 2.9%), motor neuropathy (1.1% versus 0.6%), and rash/desquamation (0.6% versus 0).

No differences in the incidence of laboratory and non-laboratory events were observed in patients 65 years or older, as compared to patients younger than 65.

6.2 Post-Marketing Experience

The following adverse reactions have been identified during post-approval use of Gemzar. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

These adverse reactions have occurred after Gemzar single-agent use and Gemzar in combination with other cytotoxic agents. Decisions to include these events are based on the seriousness of the event, frequency of reporting, or potential causal connection to Gemzar.

Cardiovascular — Congestive heart failure and myocardial infarction have been reported very rarely with the use of Gemzar. Arrhythmias, predominantly supraventricular in nature, have been reported very rarely.

Vascular Disorders — Clinical signs of peripheral vasculitis and gangrene have been reported very rarely.

Skin — Cellulitis and non-serious injection site reactions in the absence of extravasation have been rarely reported. Severe skin reactions, including desquamation and bullous skin eruptions, have been reported very rarely.

Hepatic — Increased liver function tests including elevations in aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), alkaline phosphatase, and bilirubin levels have been reported rarely. Serious hepatotoxicity including liver failure and death has been reported very rarely in patients receiving Gemzar alone or in combination with other potentially hepatotoxic drugs.

Pulmonary — Parenchymal toxicity, including interstitial pneumonitis, pulmonary fibrosis, pulmonary edema, and adult respiratory distress syndrome (ARDS), has been reported rarely following one or more doses of Gemzar administered to patients with various malignancies. Some patients experienced the onset of pulmonary symptoms up to 2 weeks after the last Gemzar dose. Respiratory failure and death occurred very rarely in some patients despite discontinuation of therapy.

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

Injury, Poisoning, and Procedural Complications — Radiation recall reactions have been reported. [see Warnings and Precautions (5.8)]

7 DRUG INTERACTIONS

No specific drug interaction studies have been conducted. Information is available on the pharmacodynamics and pharmacokinetics of Gemzar in combination with cisplatin, paclitaxel, or carboplatin. [see Clinical Pharmacology (12.2 and 12.3)]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D [see Warnings and Precautions (5.6)]

Gemzar can cause fetal harm when administered to a pregnant woman. Based on its mechanism of action, Gemzar is expected to result in adverse reproductive effects. There are no adequate and well-controlled studies of Gemzar in pregnant women.

Gemcitabine is embryotoxic causing fetal malformations (cleft palate, incomplete ossification) at doses of 1.5 mg/kg/day in mice (about 1/200 the recommended human dose on a mg/m² basis). Gemcitabine is fetotoxic causing fetal malformations (fused pulmonary artery, absence of gall bladder) at doses of 0.1 mg/kg/day in rabbits (about 1/600 the recommended human dose on a mg/m² basis). Embryotoxicity was characterized by decreased fetal viability, reduced live litter sizes, and developmental delays. 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 *Warnings and Precautions* (5.6)]

8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Gemzar, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and effectiveness of Gemzar in pediatric patients has not been established. Gemzar was evaluated in a Phase 1 trial in pediatric patients with refractory leukemia and determined that the maximum tolerated dose was 10 mg/m²/min for 360 minutes three times weekly followed by a one-week rest period. Gemzar was also evaluated in a Phase 2 trial in patients with relapsed acute lymphoblastic leukemia (22 patients) and acute myelogenous leukemia (10 patients) using 10 mg/m²/min for 360 minutes three times weekly followed by a one-week rest period. Toxicities observed included bone marrow suppression, febrile neutropenia, elevation of serum transaminases, nausea, and rash/desquamation, which were similar to those reported in adults. No meaningful clinical activity was observed in this Phase 2 trial.

8.5 Geriatric Use

Gemzar clearance is affected by age [see *Clinical Pharmacology* (12.3)]. There is no evidence, however, that unusual dose adjustments [see *Dosage and Administration* (2.1, 2.2, 2.3, and 2.4)] are necessary in patients over 65, and in general, adverse reaction rates in the single-agent safety database of 979 patients were similar in patients above and below 65. Grade 3/4 thrombocytopenia was more common in the elderly. In the randomized clinical trial of Gemzar in combination with carboplatin for recurrent ovarian cancer [see *Clinical Studies* (14.1)], 125 women treated with Gemzar plus carboplatin were <65 years and 50 were ≥65 years. Similar effectiveness was observed between older and younger women. There was significantly higher Grade 3/4 neutropenia in women 65 years of age or older. Overall, there were no other substantial differences in toxicity profile of Gemzar plus carboplatin based on age.

8.6 Renal

Hemolytic Uremic Syndrome (HUS) and/or renal failure have been reported following one or more doses of Gemzar. 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)].

Gemzar 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 *Warnings and Precautions* (5.4)]

8.7 Hepatic

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

Gemzar 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 Gemzar 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 *Warnings and Precautions* (5.5)]

8.8 Gender

Gemzar clearance is affected by gender. [see *Clinical Pharmacology* (12.3)] In the single-agent safety database (N=979 patients), however, there is no evidence that unusual dose adjustments [see *Dosage and Administration* (2)] are necessary in women. In general, in single-agent studies of Gemzar, adverse reaction rates were similar in men and women, but women, especially older women, were more likely not to proceed to a subsequent cycle and to experience Grade 3/4 neutropenia and thrombocytopenia. There was a greater tendency in women, especially older women, not to proceed to the next cycle.

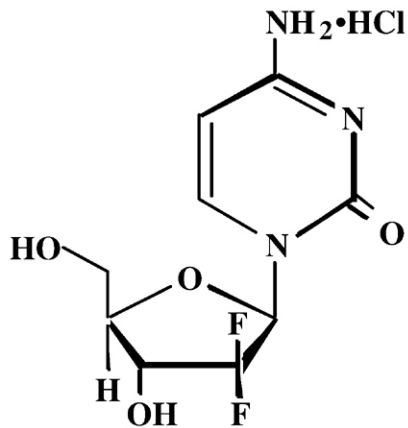
10 OVERDOSAGE

There is no known antidote for overdoses of Gemzar. Myelosuppression, paresthesias, and severe rash were the principal toxicities seen when a single dose as high as 5700 mg/m² was administered by IV infusion over 30 minutes every 2 weeks to several patients in a Phase 1 study. In the event of suspected overdose, the patient should be monitored with appropriate blood counts and should receive supportive therapy, as necessary.

11 DESCRIPTION

Gemzar (gemcitabine for injection, USP) is a nucleoside metabolic inhibitor that exhibits antitumor activity. Gemcitabine HCl is 2'-deoxy-2',2'-difluorocytidine monohydrochloride (β-isomer).

The structural formula is as follows:



The empirical formula for gemcitabine HCl is $C_9H_{11}F_2N_3O_4 \cdot HCl$. It has a molecular weight of 299.66.

Gemcitabine HCl is a white to off-white solid. It is soluble in water, slightly soluble in methanol, and practically insoluble in ethanol and polar organic solvents.

The clinical formulation is supplied in a sterile form for intravenous use only. Vials of Gemzar contain either 200 mg or 1 g of gemcitabine HCl (expressed as free base) formulated with mannitol (200 mg or 1 g, respectively) and sodium acetate (12.5 mg or 62.5 mg, respectively) as a sterile lyophilized powder. Hydrochloric acid and/or sodium hydroxide may have been added for pH adjustment.

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 deoxynucleoside triphosphates for DNA synthesis. Inhibition of this enzyme by the diphosphate nucleoside causes a reduction in the concentrations of deoxynucleotides, 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 (self-potential). After the gemcitabine nucleotide is incorporated into DNA, only one additional nucleotide is added to the growing DNA strands. After this addition, there is inhibition of further DNA synthesis. DNA polymerase epsilon is unable to remove the gemcitabine nucleotide and repair the growing DNA strands (masked chain termination). In CEM T lymphoblastoid cells, gemcitabine induces internucleosomal 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 LX-1 and CALU-6 human lung xenografts, but minimal activity was seen with the NCI-H460 or NCI-H520 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 Gemzar 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',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 Men (L/hr/m ²)	Clearance Women (L/hr/m ²)	Half-Life ^a Men (min)	Half-Life ^a 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

^a 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 638 minutes, depending on age and gender, reflecting a greatly increased volume of distribution with longer infusions.

Drug Interactions

When Gemzar (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 3.94 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, Gemzar 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 Gemzar. Data from NSCLC patients demonstrate that Gemzar and carboplatin given in combination does not alter the pharmacokinetics of Gemzar 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 Gemzar have not been conducted. Gemcitabine induced forward mutations *in vitro* in a mouse lymphoma (L5178Y) 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 hypospermatogenesis, 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 embryoletality 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

Gemzar 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 Gemzar 1000 mg/m² on Days 1 and 8 of a 21-day cycle and carboplatin AUC 4 administered after Gemzar 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 Gemzar 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 Gemzar after progression. There was not a significant difference in overall survival between arms.

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

	Gemzar/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%
Bidimensionally measurable	91.6%	95.5%
Platinum-free interval ^b		
6-12 months	39.9%	39.9%
>12 months	59.0%	59.6%
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 Gemzar 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 Gemzar plus carboplatin arm and 1 on the carboplatin arm) had a platinum-free interval of less than 6 months.

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

	Gemzar/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 ^d
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=0.8977 ^d
Hazard Ratio (95%, C.I.)	0.98 (0.78, 1.24)		
Adjusted ^a Hazard Ratio (95%, C.I.)	0.86 (0.67, 1.10)		
Investigator Reviewed			
Overall Response Rate	47.2%	30.9%	p=0.0016 ^e
CR	14.6%	6.2%	
PR+PRNM ^b	32.6%	24.7%	
Independently Reviewed			
Overall Response Rate ^{c,f}	46.3%	35.6%	p=0.11 ^e
CR	9.1%	4.0%	
PR+PRNM	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 Chi Square

^f Independently reviewed cohort - Gemzar/Carboplatin N=121, Carboplatin N=101

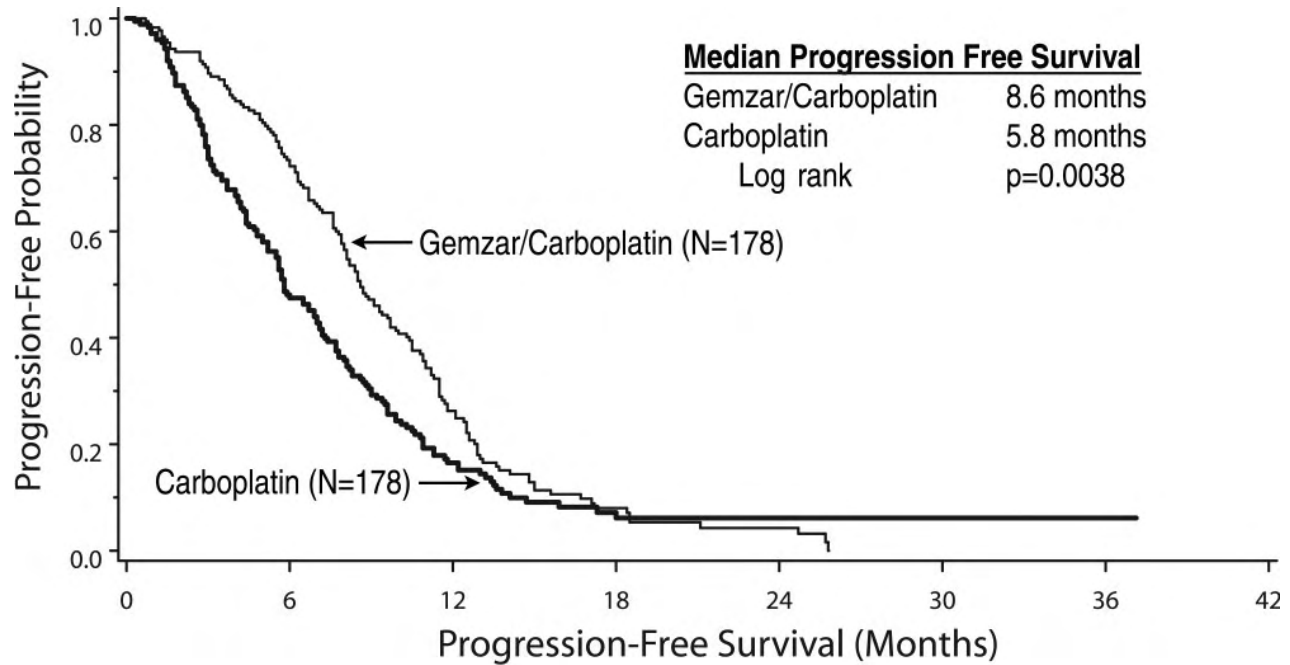


Figure 1: Kaplan-Meier Curve of Progression Free Survival in Gemzar Plus Carboplatin Versus Carboplatin in Ovarian Cancer (N=356)

14.2 Breast Cancer

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

Table 12: Gemzar Plus Paclitaxel Versus Paclitaxel in Breast Cancer

	Gemzar/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			p<0.0001
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)		p<0.0001
Overall Response Rate ^c			p<0.0001
(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.

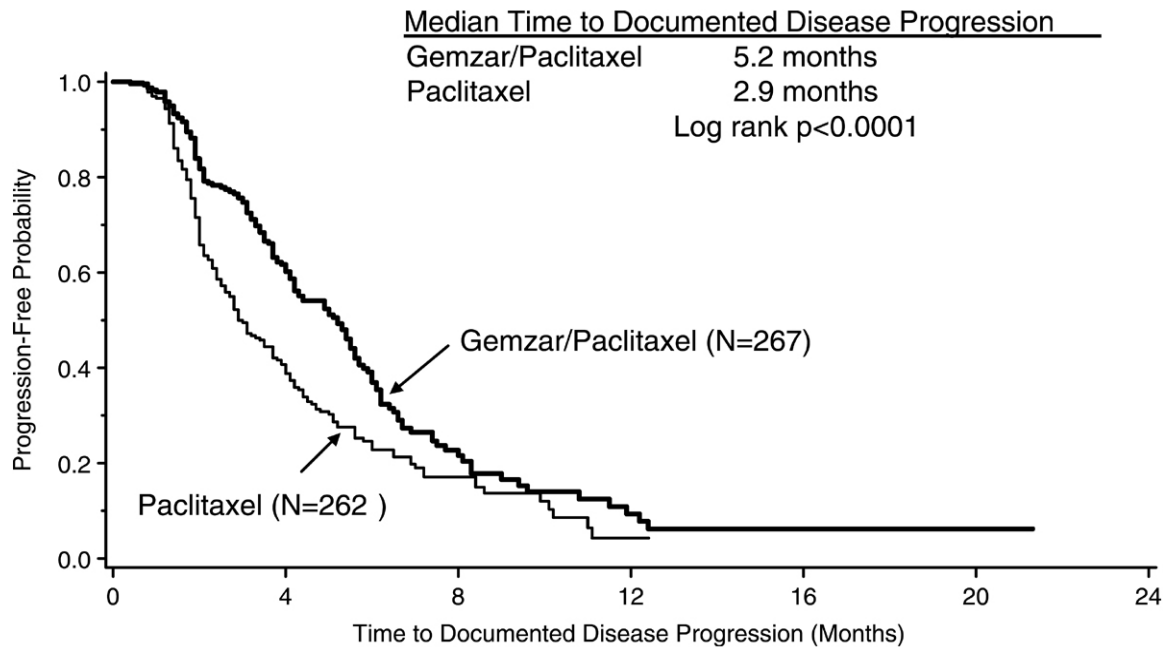


Figure 2: Kaplan-Meier Curve of Time to Documented Disease Progression in Gemzar Plus Paclitaxel Versus Paclitaxel Breast Cancer Study (N=529)

14.3 Non-Small Cell Lung Cancer (NSCLC)

Data from 2 randomized clinical studies (657 patients) support the use of Gemzar in combination with cisplatin for the first-line treatment of patients with locally advanced or metastatic NSCLC.

Gemzar 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. Gemzar 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 Gemzar plus cisplatin arm having adenocarcinoma.

The Kaplan-Meier survival curve is shown in Figure 3. Median survival time on the Gemzar plus cisplatin arm was 9.0 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 Gemzar plus cisplatin arm compared to 3.7 months on the cisplatin arm (Log rank $p = 0.009$, two-sided). The objective response rate on the Gemzar 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.

Gemzar plus cisplatin versus etoposide plus cisplatin: A second, multicenter, study in Stage IIIB or IV NSCLC randomized 135 patients to Gemzar 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 Gemzar plus cisplatin arm versus 7.0 months for the etoposide plus cisplatin arm. Median time to disease progression for the Gemzar 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 Gemzar 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 Gemzar 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 Gemzar 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 Gemzar plus cisplatin arm and the comparator arm.

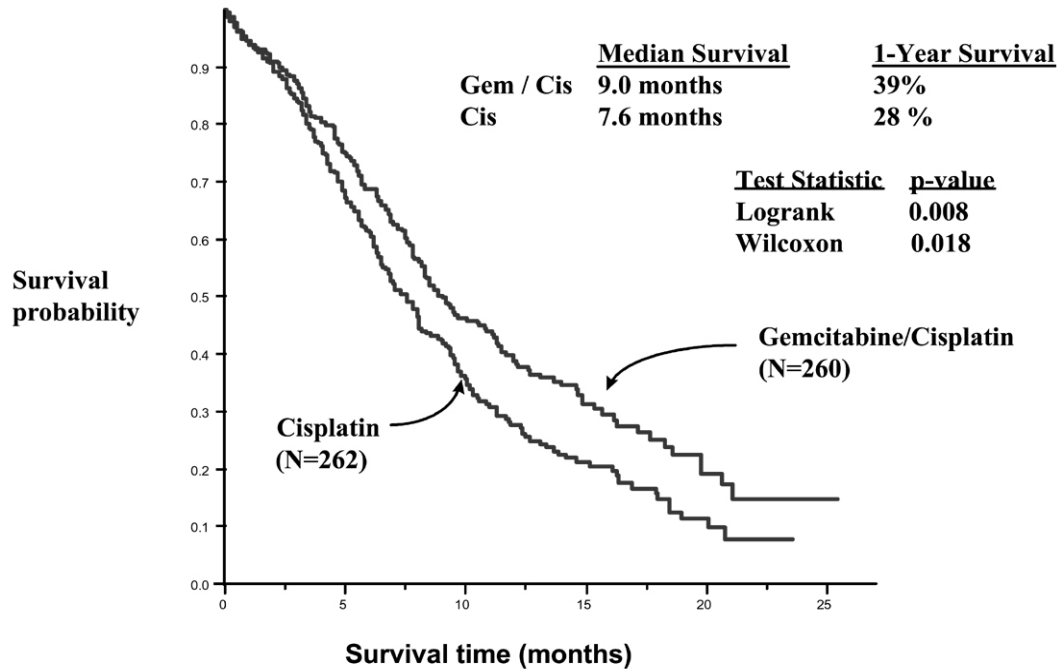


Figure 3: Kaplan-Meier Survival Curve in Gemzar Plus Cisplatin Versus Cisplatin NSCLC Study (N=522)

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

Trial	28-day Schedule ^a		21-day Schedule ^b		
	Gemzar/Cisplatin	Cisplatin	Gemzar/Cisplatin	Cisplatin/Etoposide	
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	p=0.008	8.7	7.0
(95%, C.I.) months	8.2, 11.0	6.6, 8.8		7.8, 10.1	6.0, 9.7
Time to Disease Progression			p=0.009		p=0.015
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, 4.5
Tumor Response	26%	10%	p<0.0001 ^e	33%	14%
					p=0.01 ^e

^a 28-day schedule — Gemzar plus cisplatin: Gemzar 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 — Gemzar plus cisplatin: Gemzar 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 Gemzar in patients with locally advanced or metastatic pancreatic cancer. The first trial compared Gemzar to 5-Fluorouracil (5-FU) in patients who had received no prior chemotherapy. A second trial studied the

use of Gemzar in pancreatic cancer patients previously treated with 5-FU or a 5-FU-containing regimen. In both studies, the first cycle of Gemzar 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 Gemzar. 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 $\geq 50\%$ reduction in pain intensity (Memorial Pain Assessment Card) or analgesic consumption, or a 20-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 20-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 ($\geq 7\%$ increase maintained for ≥ 4 weeks) not due to fluid accumulation.

The first study was a multicenter (17 sites in US and Canada), prospective, single-blinded, two-arm, randomized, comparison of Gemzar 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 Gemzar 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: Gemzar Versus 5-FU in Pancreatic Cancer

	Gemzar	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 ^c =14)	4.8% (N ^c =3)	p=0.004 ^c
Survival			p=0.0009
Median	5.7 months	4.2 months	
6-month probability ^b	(N=30) 46%	(N=19) 29%	
9-month probability ^b	(N=14) 24%	(N=4) 5%	
1-year probability ^b	(N=9) 18%	(N=2) 2%	
Range	0.2 to 18.6 months	0.4 to 15.1+ ^d 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+ ^d to 9.4 months	0.1 to 12.0+ ^d 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 Gemzar and 3 patients treated with 5-FU. One patient on the Gemzar arm showed improvement in all 3 primary parameters (pain intensity, analgesic consumption, and performance status). Eleven patients on the Gemzar 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 Gemzar 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.

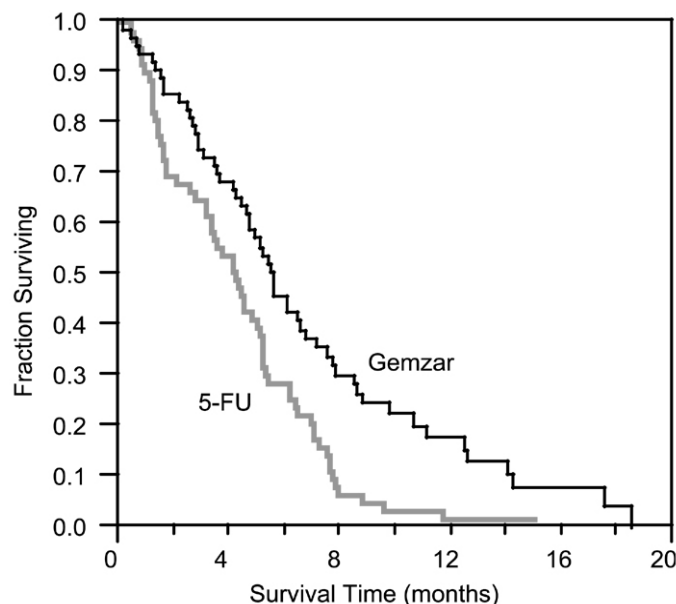


Figure 4: Kaplan-Meier Survival Curve

The second trial was a multicenter (17 US and Canadian centers), open-label study of Gemzar 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 Gemzar 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 Gemzar 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 asthenia. In a Phase 1 study to assess the maximum tolerated infusion time, clinically significant toxicity, defined as myelosuppression, 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 Gemzar is administered more frequently than once weekly or with infusions longer than 60 minutes [see *Warnings and Precautions* (5.1)].

15 REFERENCES

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3. American Society of Health-System Pharmacists. ASHP Guidelines on Handling Hazardous Drugs: *Am J Health-Syst Pharm.* 2006;63:1172-1193.
4. Polovich, 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

GEMZAR (gemcitabine for injection, USP), is available in sterile single-use vials individually packaged in a carton containing:

200 mg white to off-white, lyophilized powder in a 10-mL size sterile single-use vial - NDC 0002-7501-01 (No. 7501)

1 g white to off-white, lyophilized powder in a 50-mL size sterile single-use vial - NDC 0002-7502-01 (No. 7502)

16.2 Storage and Handling

Unopened vials of Gemzar 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° and 30°C (59° and 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 (5.2)]

17.2 Pregnancy

There are no adequate and well-controlled studies of Gemzar in pregnant women. Based on animal studies Gemzar 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) and Use in Specific Populations (8.1)]

17.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Gemzar, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. [see Use in Specific Populations (8.3)]

Literature revised Month dd, yyyy

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