GEMCITABINE (Systemic)

Antineoplastic .

Indications

Note: Bracketed information in the Indications section refers to uses that are not included in U.S. product labeling.

Accepted

Carcinoma, pancreatic (treatment)¾Gemcitabine is indicated as first-line therapy for locally advanced (nonresectable Stage II or III) or metastatic (Stage IV) adenocarcinoma of the pancreas. 1 It is also indicated as second-line therapy for patients who have previously been treated with fluorouracil. 1 Treatment with gemcitabine is primarily palliative. 13

Carcinoma, lung, non-small cell¾Gemcitabine is indicated in combination with cisplatin 1 as first-line therapy for inoperable, locally advanced (Stage IIIA or IIIB) or metastatic (Stage IV) non-small cell lung carcinoma. 2, 3, 4, 5, 6, 13

[Carcinoma, bladder] *¾Gemcitabine is indicated for treatment of metastatic bladder (urothelial) carcinoma, based on response rates (both complete and partial responses) achieved in clinical trials. 18, 19, 20, 21, 22

[Carcinoma, breast (treatment) ] *¾Gemcitabine is indicated, alone or in combination with other chemotherapeutic agents, as reasonable medical therapy at some point in the management of patients with advanced or metastatic breast carcinoma (Evidence rating: IIID). 23

[Carcinoma, ovarian, epithelial (treatment) ] *¾Gemcitabine is indicated, alone or in combination with other chemotherapeutic agents, as reasonable medical therapy at some point in the management of patients with advanced or relapsed epithelial ovarian carcinoma (Evidence rating: IIID). 23

Precautions to Consider

Carcinogenicity

Secondary malignancies are potential delayed effects of many antineoplastic agents, although it is not clear whether the effect is related to their mutagenic or immunosuppressive action. The effect of dose and duration of therapy is also unknown, although risk seems to increase with long-term use. 10 The risk of secondary malignancies developing after gemcitabine therapy is not known. 15

Long-term animal studies to evaluate the carcinogenic potential of gemcitabine have not been done. 1, 2

Mutagenicity

Gemcitabine was mutagenic in in vitro (mouse lymphoma assay) and in vivo (mouse micronucleus assay) mammalian test systems. However, it was not mutagenic in the Ames test, in vivo sister chromatid exchange, or in in vitro (chromosomal aberration assays and unscheduled DNA synthesis) test systems. 1

Pregnancy/Reproduction

Fertility¾Intraperitoneal administration to male mice of 0.5 mg per kg of body weight (mg/kg) per day (0.14% of the recommended human dose on a mg per square meter of body surface area [mg/m 2] basis) resulted in moderate to severe 1 hypospermatogenesis 1, 2 , decreased fertility 1 , and decreased implantations 1.

The hypospermatogenesis was reversible. 2 Gemcitabine did not impair fertility 1, 2 , but caused maternal toxicity in female mice given doses of 1.5 mg/kg per day (0.5% of the recommended human dose on a mg/m 2 basis) 1.

Pregnancy¾:

Studies in humans have not been done. 1

It is usually recommended that use of antineoplastics, especially combination chemotherapy, be avoided whenever possible, especially during the first trimester. Although information is limited because of the relatively few instances of antineoplastic administration during pregnancy, the mutagenic, teratogenic, and carcinogenic potential of these medications must be considered. 10

Other potential hazards to the fetus include adverse reactions seen in adults. 10

In general, use of a contraceptive is recommended during therapy with cytotoxic medications. 10

Gemcitabine caused fetal malformations (fusion of the pulmonary artery and absence of the gallbladder) in rabbits given 0.1 mg/kg per day (0.17% of the recommended human dose on a mg/m 2 basis). The medication was embryotoxic (causing decreased fetal viability, reduced live litter sizes, and delayed development), and teratogenic (causing cleft palate and incomplete ossification) in mice given 1.5 mg/kg per day (0.5% of the recommended human dose on a mg/m 2 basis). In mice, embryolethality or fetotoxicity occurred with intravenous doses as low as 0.25 mg/kg per day (0.08% of the recommended human dose on a mg/m 2 basis). 1

FDA Pregnancy Category D. 1

Breast-feeding

Although very little information is available regarding distribution of antineoplastic agents into breast milk, breast-feeding is not recommended while gemcitabine is being administered, because of the risks to the infant (adverse effects, mutagenicity, carcinogenicity). 10 It is not known whether gemcitabine or its metabolites are distributed into breast milk. 1, 2

Pediatrics

Appropriate studies on the relationship of age to the effects of gemcitabine have not been performed in the pediatric population. Safety and efficacy have not been established. 1

Geriatrics

Appropriate studies performed to date have not demonstrated geriatrics-specific problems that would limit the usefulness of gemcitabine in the elderly. 4 Although some pharmacokinetic parameters are altered in geriatric patients (increased elimination half-life and decreased clearance), no adjustment of the initial dose is recommended for patients older than 65 years of age. 1, 2 However, the risk of hematologic toxicity requiring reduction, delay, or omission of subsequent doses is higher in elderly patients than in younger adults. 1 Specifically, Grade 3 or 4 thrombocytopenia is more likely to occur in elderly men and women and Grade 3 or 4 neutropenia is more likely to occur in elderly women. 1 Nonhematologic toxicities did not occur more frequently in patients older than 65 years of age than in younger adults. 4

Dental

The bone marrow depressant effects of gemcitabine may result in an increased incidence of microbial infection, delayed healing, and gingival bleeding. Dental work, whenever possible, should be completed prior to initiation of therapy or deferred until blood counts have returned to normal. Patients should be instructed in proper oral hygiene during treatment, including caution in use of regular toothbrushes, dental floss, and toothpicks. 10

Gemcitabine causes stomatitis 1, 2 , usually mild 2 , in a minority of patients (incidence 11% 1 or lower 2 in various clinical trials).

Drug interactions and/or related problems

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):
Blood dyscrasia-causing medications (see Appendix II )

(leukopenic and/or thrombocytopenic effects of gemcitabine may be increased with concurrent or recent therapy if these medications cause the same effects; dosage adjustment of gemcitabine, if necessary, should be based on blood counts 10 )

>> Bone marrow depressants, other (see Appendix II ) or

>> Radiation therapy

(additive bone marrow depression may occur; dosage reduction may be required when two or more bone marrow depressants, including radiation, are used concurrently or consecutively 10 )
(gemcitabine is a potent 8, 9 radiosensitizer 2, 8, 9 ; depending on the site being irradiated, concurrent use of gemcitabine may cause severe, life-threatening esophagitis or pneumonitis 1, 2 ; in one study, gemcitabine with radiation therapy caused severe stomatitis or pharyngeal damage requiring patients to be fed via feeding tube for as long as 10 to 12 months, even when gemcitabine was given in doses as low as 300 mg per square meter of body surface area [25% or less of the usual adult dose] 11 )

>> Immunosuppressants, other, such as:
Azathioprine
Chlorambucil
Corticosteroids, glucocorticoid
Cyclophosphamide
Cyclosporine
Mercaptopurine
Muromonab CD-3
Tacrolimus

Side/Adverse Effects

Note: Many "side effects" of antineoplastic therapy are unavoidable and represent the medication's pharmacologic action. Some of these (for example, leukopenia and thrombocytopenia) are actually used as parameters to aid in individual dosage titration. 10

The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)¾not necessarily inclusive:
Those indicating need for medical attention