

Only physicians experienced in cancer chemotherapy should use Cytarabine Injection.

The physician must judge possible benefit to the patient against known toxic effects of this drug in considering the advisability of therapy with Cytarabine Injection. Before making this judgment or beginning treatment, the physician should be familiar with the following text.

Cytarabine Injection, an antineoplastic, is a sterile solution of cytarabine for intravenous, intrathecal or subcutaneous administration. Each mL contains 100 mg cytarabine USP in 2 g/20 mL (100 mg/mL) single dose vial and the following inactive ingredients: water for injection q.s. When necessary the pH is adjusted with hydrochloric acid and/or sodium hydroxide to a pH of 7.7.

NC1=NC(=O)N2C(=O)C(O)C(O)C2=N1

M.W. 243.22

CLINICAL PHARMACOLOGY:

Cytarabine is cytotoxic to a wide variety of proliferating mammalian cells in culture. It exhibits cell phase specificity, primarily killing cells undergoing DNA synthesis (S-phase) and under certain conditions blocking the progression of cells from the G1 phase to the S-phase. Although the mechanism of action is not completely understood, it appears that cytarabine acts through the inhibition of DNA polymerase. A limited, but significant, incorporation of cytarabine into both DNA and RNA has also been reported. Extensive chromosomal damage, including chromatoid breaks, have been produced by cytarabine and malignant transformation of rodent cells in culture has been reported. Deoxycytidine prevents or delays (but does not reverse) the cytotoxic activity.

Cytarabine is metabolized by deoxycytidine kinase and other nucleotide kinases to the nucleotide triphosphate, an effective inhibitor of DNA polymerase; it is inactivated by a pyrimidine nucleoside deaminase, which converts it to the non-toxic uracil derivative. It appears that the balance of kinase and deaminase levels may be an important factor in determining sensitivity or resistance of the cell to cytarabine.

Cytarabine is rapidly metabolized and is not effective orally; less than 20 percent of the orally administered dose is absorbed from the gastrointestinal tract.

Cerebrospinal fluid levels of cytarabine are low in comparison to plasma levels after single intravenous injection. However, in one patient in whom cerebrospinal fluid levels are examined after 2 hours of constant intravenous infusion, levels approached 40 percent of the steady state plasma level. With intrathecal administration, levels of cytarabine in the cerebrospinal fluid declined with a first order half-life of about 2 hours. Because cerebrospinal fluid levels of deaminase are low, little conversion to ara-U was observed.

Cytarabine Injection is capable of obliterating immune responses in man during administration with little or no accompanying toxicity. Suppression of antibody responses to E-coli-VI antigen and tetanus toxoid have been demonstrated. This suppression was obtained during both primary and secondary antibody responses.

Following 5-day courses of intensive therapy with cytarabine the immune response was suppressed, as indicated by the following parameters: macrophage ingress into skin windows; circulating antibody response following primary antigenic stimulation; lymphocyte blastogenesis with phytohemagglutinin. A few days after termination of therapy there was a rapid return to normal.

Cytarabine Injection is contraindicated in those patients who are hypersensitive to the drug.

Cytarabine is a potent bone marrow suppressant. Therapy should be started cautiously in patients with pre-existing drug-induced bone marrow suppression. Patients receiving this drug must be under close medical supervision and, during induction therapy, should have leucocyte and platelet counts performed daily. Bone marrow examinations should be performed frequently after blasts have disappeared from the peripheral blood. Facilities should be available for management of complications, possibly fatal, of bone marrow suppression (infection resulting from granulocytopenia and other impaired body defenses, and hemorrhage secondary to thrombocytopenia). One case of anaphylaxis

Because of the potential for abnormalities with cytotoxic therapy, particularly during the first trimester, a patient who is or who may become pregnant while on cytarabine should be apprised of the potential risk to the fetus.

Extensive chromosomal damage, including chromatoid breaks have been produced by cytarabine and malignant transformation of rodent cells in culture has been reported.

Severe and at times fatal CNS, GI and pulmonary toxicity (different from that seen with conventional therapy regimens of cytarabine)

has been reported following some experimental dose schedules of cytarabine. These reactions include reversible corneal toxicity and hemorrhagic conjunctivitis, which may be prevented or diminished by prophylaxis with a local corticosteroid eye drop; cerebral and cerebellar dysfunction, including personality changes, somnolence and coma, usually reversible; severe gastrointestinal ulceration, including pneumatosis cystoides intestinalis leading to peritonitis; sepsis and liver abscess; pulmonary edema, liver damage with increased hyperbilirubinemia; bowel necrosis; and necrotizing colitis. Rarely, severe skin rash, leading to desquamation has been reported. Complete alopecia is more commonly seen with experimental high dose therapy than with standard treatment programs using cytarabine. If experimental high dose therapy is used, do not use a preparation containing benzyl alcohol.

Cases of cardiomyopathy with subsequent death have been reported following experimental high dose therapy with cytarabine in combination with cyclophosphamide when used for bone marrow transplant preparation.

This cardiac toxicity may be schedule dependent.

A syndrome of sudden respiratory distress, rapidly progressing to pulmonary edema and radiographically pronounced cardiomegaly has been reported following experimental high dose therapy with cytarabine used for the treatment of relapsed leukemia from one institution in 16/72 patients. The outcome of this syndrome can be fatal.

Two patients with adult acute non-lymphocytic leukemia developed peripheral motor and sensory neuropathies after consolidation with high-dose cytarabine, daunorubicin, and asparaginase. Patients treated with high-dose cytarabine should be observed for neuropathy since dose schedule alterations may be needed to avoid irreversible neurologic disorders.

Ten patients treated with experimental intermediate doses of cytarabine (1 g/m²) with and without other chemotherapeutic agents (meta-AMSA, daunorubicin, etoposide) at various dose regimes developed a diffuse interstitial pneumonitis without clear cause that may have been related to the cytarabine.

Two cases of pancreatitis have been reported following experimental doses of cytarabine and numerous other drugs. Cytarabine could have been the causative agent.

To report SUSPECTED ADVERSE REACTIONS, contact Fresenius Kabi USA, LLC at 1-800-551-7176 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

OVERDOSAGE:

There is no antidote for overdosage of cytarabine. Doses of 4.5 g/m² by intravenous infusion over 1 hour every 12 hours for 12 doses have caused an unacceptable increase in irreversible CNS toxicity and death.

Single doses as high as 3 g/m² have been administered by rapid intravenous infusion without apparent toxicity.

DOSAGE AND ADMINISTRATION:

Cytarabine Injection is not active orally. The schedule and method of administration varies with the program of therapy to be used. Cytarabine Injection may be given by intravenous infusion or injection, subcutaneously, or intrathecally (preservative free preparation only).

Thrombophlebitis has occurred at the site of drug injection or infusion in some patients, and rarely patients have noted pain and inflammation at subcutaneous injection sites. In most instances, however, the drug has been well tolerated.

Patients can tolerate higher total doses when they receive the drug by rapid intravenous injection as compared with slow infusion. This phenomenon is related to the drug's rapid inactivation and brief exposure of susceptible normal and neoplastic cells to significant levels after rapid injection. Normal and neoplastic cells

seem to respond in somewhat parallel fashion to these different modes of administration and no clear-cut clinical advantage has been demonstrated for either.

In the induction therapy of acute non-lymphocytic leukemia, the usual cytarabine dose in combination with other anticancer drugs is 100 mg/m²/day by continuous IV infusion (Days 1 to 7) or 100 mg/m² IV every 12 hours (Days 1 to 7).

The literature should be consulted for the current recommendations for use in acute lymphocytic leukemia.

Intrathecal Use in Meningeal Leukemia

Cytarabine Injection has been used intrathecally in acute leukemia in doses ranging from 5 mg/m² to 75 mg/m² of body surface area. The frequency of administration varied from once a day for 4 days to once every 4 days. The most frequently used dose was 30 mg/m² every 4 days until cerebrospinal fluid findings were normal, followed by one additional treatment. The dosage schedule is usually governed by the type and severity of central nervous system manifestations and the response to previous therapy.

Cytarabine Injection given intrathecally may cause systemic toxicity and careful monitoring of the hematopoietic system is indicated. Modification of other anti-leukemia therapy may be necessary. Major toxicity is rare. The most frequently reported reactions after intrathecal administration were nausea, vomiting, and fever; these reactions are mild and self-limiting. Paraplegia has been reported. Necrotizing leukoencephalopathy occurred in 5 children; these patients had also been treated with intrathecal methotrexate and hydrocortisone, as well as by central nervous system radiation. Isolated neurotoxicity has been reported. Blindness occurred in two patients in remission whose treatment had consisted of combination systemic chemotherapy, prophylactic central nervous system radiation and intrathecal Cytarabine Injection.

When Cytarabine Injection is administered both intrathecally and intravenously within a few days, there is an increased risk of spinal cord toxicity, however, in serious life-threatening disease, concurrent use of intravenous and intrathecal Cytarabine Injection is left to the discretion of the treating physician.

Focal leukemic involvement of the central nervous system may not respond to intrathecal Cytarabine Injection and may better be treated with radiotherapy.

Chemical Stability of Infusion Solutions

Chemical stability studies were performed by HPLC on Cytarabine Injection in infusion solutions. These studies showed that when Cytarabine Injection was added to Water for Injection, 5% Dextrose in Water or Sodium Chloride Injection, 94 to 96 percent of the cytarabine was present after 192 hours storage at room temperature.

Parenteral drugs should be inspected visually for particulate matter and discoloration, prior to administration, whenever solution and container permit.

If a precipitate has formed as a result of exposure to low temperatures, redissolve by warming up to 55°C for no longer than 30 minutes, under dry heat conditions, and shake until the precipitate has dissolved.

HANDLING AND DISPOSAL:

Procedures for proper handling and disposal of anti-cancer drugs should be considered. Several guidelines on this subject have been published.¹⁻⁷ There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

HOW SUPPLIED:

Product No.	NDC No.	
102020	63323-120-20	Cytarabine Injection, 2 g per 20 mL (100 mg per mL) sterile solution in a single dose flip cap vial, packaged individually.

The container closure is not made with natural rubber latex.

STORAGE CONDITIONS:

Protect from light (keep in outer carton).

Store at 20°C to 25°C (68°F to 77°F) [see USP Controlled Room Temperature]. Do not refrigerate.

REFERENCES:

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2. AMA Council Report, Guidelines for Handling Parenteral Antineoplastics, JAMA, 1985; 2:53 (11): 1590-1592.
3. National Study Commission on Cytotoxic Exposure-Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, ScD., Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, Massachusetts 02115.
4. Clinical Oncological Society of Australia, Guidelines and Recommendations for Safe Handling of Antineoplastic Agents. Med J Australia, 1983; 1:426-428.
5. Jones RB, et al: Safe Handling of Chemotherapeutic Agents: A Report from the Mount Sinai Medical Center. CA-A Cancer Journal of Clinicians, 1983; (Sept/Oct) 258-263.
6. American Society of Hospital Pharmacists Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs. Am J. Hosp. Pharm, 1990; 47:1033-1049.
7. Controlling Occupational Exposure to Hazardous Drugs. (OSHA Work Practice Guidelines), Am J. Health-Syst Pharm, 1996; 53:1669-1685.



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