Cytarabine for Injection USP

DESCRIPTION

Cytarabine for Injection, USP, commonly known as ara-C, is an antineoplastic, is a sterile lyophilized material for reconstitution and intravenous, intrathecal or subcutaneous administration. It is available in multi-dose vials containing 100 mg, 500 mg, 1 g or 2 g sterile cytarabine. The pH of Cytarabine for Injection, USP, was adjusted, when necessary, with hydrochloric acid and/or sodium hydroxide.

Cytarabine is chemically 4-amino-1-D-ribofuranosyl-2-(1H)-pyrimidine. The structural formula is:

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\begin{align*}
\text{C}_{9}\text{H}_{13}\text{N}_{3}\text{O}_{5} \quad \text{Molecular weight: 243.22} \\
\text{Molecular formula: C}_{9}\text{H}_{13}\text{N}_{3}\text{O}_{5} \\
\end{align*}
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Cytarabine is an odorless, white to off-white, crystalline powder which is freely soluble in water and slightly soluble in alcohol and in chloroform.

CLINICAL PHARMACOLOGY

Cell Culture Studies
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- to the G2-phase. 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 chromatid breaks, have been produced by cytarabine and malignant transformation of rodent cells in culture has been reported. Desoxycytidine prevents or delays (but does not reverse) the cytotoxic activity.

Cellular Resistance and Sensitivity
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 pyrimidined nucleoside deaminase, which converts it to the nontoxic 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.

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

Following rapid intravenous injection of cytarabine labeled with tritium, the disappearance from plasma is biphasic. There is an initial distributive phase with a half-life of about 10 minutes, followed by a second elimination phase with a half-life of about 1 to 3 hours. After the distributive phase, more than 80 percent of plasma radioactivity can be accounted for by the inactive metabolite 1-beta-D-arabinofuranosylcytosine (ara-UA). Within 24 hours about 88 percent of the administered radioactivity can be recovered in the urine, approximately 90 percent of which is excreted as ara-U.

Relative constant plasma levels can be achieved by continuous intravenous infusion.

After subcutaneous or intramuscular administration of cytarabine labeled with tritium, peak-plasma levels of radioactivity are achieved about 20 to 90 minutes after injection and are considerably lower than those after intravenous administration. Cerebrospinal fluid levels of cytarabine are low in comparison to plasma levels after single intravenous administration. However, in one patient in whom cerebrospinal levels were examined after 2 hours of constant intravenous infusion, levels approached 40 percent of the steady state plasma level. With intrathecal administration, the cerebrospinal fluid 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 is observed.

Immunosuppressive Action
Cytarabine is capable of inhibiting immune responses in man and in man with leukemia. It also has no accompanying toxicity. Suppression of antibody responses to E. coli-VI antigen and tetanus toxoid has been demonstrated. This suppression was observed during both primary and secondary antibody responses.

Cytarabine also suppressed the development of cell-mediated immune responses such as delayed hypersensitivity skin reaction to dinitrochlorobenzene. However, it had no effect on already established delayed hypersensitivity reactions.

Following 5-day courses of intensive therapy with Cytarabine for Injection, USP, the immune response was suppressed, as indicated by the following parameters: macrophage ingression 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.

INDICATIONS AND USAGE
Cytarabine for Injection in combination with other approved anticancer drugs is indicated for remission induction in acute non-lymphocytic leukemia of adults and pediatric patients. It has also been found useful in the treatment of chronic myelogenous leukemia and the blast phase of chronic myelogenous leukemia. Intrathecal administration of Cytarabine for Injection is indicated in the prophylaxis and treatment of meningeal leukemia.

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

WARNINGS (See boxed WARNING)
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 initial therapy, blood counts should be performed at least 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 that resulted in acute coronary artery arrythmia and required resuscitation has been reported. This occurred immediately after the intravenous administration of Cytarabine for Injection, USP.

Severe and at times fatal CNS, GI and pulmonary toxicity (different from that seen with conventional therapy) of Cytarabine), has been reported following some experimental dose schedules for 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 personal dissociation, confusion, or delirium, severe gastrointestinal ulceration, including pepticusis enterocolitis leading to peritonitis; sepsis and liver abscesses; 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 in experimental high dose therapy is used, do not use a diluent 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 transplantation studies. A syndrome of sudden respiratory distress, rapidly progressing to pulmonary edema and radiographically pronounced cardiomyopathy 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.

Benzyl alcohol is contained in the diluent for this product. Benzyl alcohol has been reported to be associated with a “fetal Gating Syndrome” in premature infants.

Two patients with childhood acute myelogenous leukemia who received intrathecal and intravenous Cytarabine at conventional doses (in addition to a number of other concomitantly administered drugs) developed delayed progressive ascending paralysis resulting in death in one of the two patients.

Use in Pregnancy
Cytarabine can cause fetal harm when administered to a pregnant woman. Cytarabine causes abnormal cerebellar development in the neonatal hamster and is teratogenic to the rat fetus. There are no adequate and well-controlled studies in pregnant women. Women of childbearing potential should be advised to avoid becoming pregnant.

Pregnancy (Category D)
A review of the literature has shown 32 reported cases where Cytarabine was given during pregnancy, either alone or in combination with other cytotoxic agents.

Eighteen normal infants were delivered. Four of these had first trimester exposure. Five infants were premature or of low birth weight. Twelve of the 18 normal infants were followed up at least 6 weeks to seven years, and showed no abnormalities. One apparently normal infant died at 90 days of gastroenteritis.

Two cases of congenital abnormalities have been reported, one with upper and lower distal limb defects, and the other with extremity and ear deformities. Both of these cases had first trimester exposure.

There were seven infants with various problems in the neonatal period, including pancytopenia; transient depression of hematopoiesis; hematocrit or platelets; electrolyte abnormalities; transient eosinophilia; and one case of increased IgM levels and hypergammaglobulinemia possibly due to sepsis. Six of the seven infants were also premature. The child with pancytopenia died at 21 days of sepsis.

Therapeutic abortions were done in five cases. Four fetuses were grossly normal, but one had an enlarged spleen and another showed Trisomy C chromosome abnormality in the chorionic tissue.

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. If the patient becomes pregnant while taking this product, there is a definite, but considerably reduced risk if therapy is initiated during the second or third trimester. Although normal infants have been delivered to patients treated in all three trimesters of pregnancy, follow-up of such infants would be advisable.

PRECAUTIONS
1. General Precautions
Patients receiving Cytarabine must be monitored closely. Frequent platelet and leucocyte counts and bone marrow examinations are mandatory. Consider suspending or modifying therapy when drug-induced marrow depression results in a platelet count under 50,000 or a granulocyte count under 1000/mm3. Counts of formed elements in the peripheral blood may continue to fall after the drug is stopped and reach lowest values after drug-free intervals of 12 to 24 days. When indicated, restart therapy when definite signs of marrow recovery appear (on successive bone marrow studies). Patients whose drug is withheld until “normal” peripheral blood values are attained may escape from control.

When large intravenous doses are given quickly, patients are frequently nauseated and may vomit for several hours postinjection. This problem tends to be less severe when the drug is infused.

The human liver apparently destroys a substantial dose of administered Cytarabine. In particular, patients with renal or hepatic function impairment may have a higher likelihood of CNS toxicity after high-dose Cytarabine treatment. Use the drug with caution and possibly at reduced dose in patients whose liver or kidney function is impaired.

Peripheral checks of bone marrow, liver and kidney functions should be performed in patients receiving Cytarabine.

Like other cytotoxic drugs, Cytarabine may induce hyperuricemia, secondary to rapid lysis of neoplastic cells. The clinician should monitor the patient’s blood uric acid level and be prepared to use such supportive and pharmacologic measures as might be necessary to control this problem.

Acute pancreatitis has been reported to occur in a patient receiving Cytarabine for injection by continuous infusion and in patients being treated with Cytarabine for Injection who have had prior treatment with L-asparaginase.

2. Information for patient
Not applicable.

3. Laboratory Test
See General Precautions.

4. Drug Interactions
Reversible decreases in steady-state plasma digoxin concentrations and renal glycoside excretion were observed in patients receiving beta-salicyldehyde and chemotherapy regimens containing cyclophosphamide, vincristine and prednisone with or without Cytarabine or procarbazine. Steady-state plasma digoxin concentrations did not appear to change. Therefore, monitoring of plasma
digoxin levels may be indicated in patients receiving similar combination chemotherapy regimens. The utilization of digoxin for such patients may be considered as an alternative.

An in vitro interaction study between gentamicin and cytarabine showed a cytarabine related antagonism for the susceptibility of a K. pneumoniae strain. This study suggests that in patients on cytarabine being treated with gentamicin for a K. pneumoniae infection, the lack of a prompt therapeutic response may indicate the need for reevaluation of antibacterial therapy. Clinical evidence in one patient showed possible inhibition of fluocoxacin efficacy during therapy with Cytarabine. This may be due to potential competitive inhibition of its uptake.

5. Carcinogenesis, Mutagenesis, Impairment of Fertility. Extensive chromosomal damage with chromatid breaks have been produced by cytarabine and malignant transformation of rodent cells in culture has been reported.

6. Pregnancy

Pregnancy Category D. See WARNINGS. Labor and delivery. Not applicable. 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 cytarabine, 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.

9. Pediatric Use

See INDICATIONS AND USAGE

Expected Reactions

Because cytarabine is a bone marrow suppressant, anemia, leukopenia, thrombocytopenia, megaloblastosis and reducible reticulocytes can be expected as a result of administration with Cytarabine. The severity of these reactions are dose and schedule dependent. Cellular changes in the morphology of bone marrow and peripheral smears can be expected.

Following 5-day constant infusions or acute injections of 50 mg/m ² to 750 mg/m ² while cell division follows a biphasic course. Regression of initial count, dose level, schedule, there is an initial fall starting the first 24 hours with a nadir at days 7-9. This is followed by a rise which peaks around the twelfth day. The second and deepest advances nadir at days 15-24. There is then a rapid rise to above baseline in the next 10 days. Platelet depression is noticeable at 5 days with a peak depression occurring between days 12-15. Therefore, a rapid rise to above baseline occurs in the next 10 days.

Infecetous Complications

Viral, bacterial, fungal, parasitic, or opportunistic infections, in any location in the body may be associated with the use of Cytarabine for Injection. USP alone or in combination with other immunosuppressive agents following immunosuppressive doses that affect cellular or humoral immunity. These infections may be mild, but can be severe and at times fatal.

The Cytarabine (Ar-C) Syndrome

A cytarabine syndrome has been described by Castleberry. It is characterized by fever, myalgia, bone pain, occasionally seizures, heart rate, pulmonary edema, rash, conjunctival signs, and malaise. It usually occurs 6 to 12 hours following drug administration. Corticosteroids have been shown to be beneficial in treating or preventing this syndrome. If the symptoms of the syndrome are deemed treatable, corticosteroids should be contemplated as well as continuation of therapy with Cytarabine.

Most Frequent Adverse Reactions

anorexia nausea vomiting diarrhea oral and anal inflammation hepatic dysfunction urticaria or ulceration bleeding (all sites) fever alopecia conjunctivitis keratitis pyrexia alopecia rash pruritus alopecia pruritus atriotonia anaphylaxis (see WARNINGS) alopecia orthostatic hypotension alopecia alopecia alopecia alopecia alopecia alopecia alopecia alopecia alopecia alopecia alopecia alopecia alopecia alopecia alopecia alopecia alopecia alopecia alopecia alopecia alopecia alopecia alopecia alopecia alopecia alopecia alopecia alopecia alopecia alopecia alopecia alopecia alopecia alopecia alopecia alopecia alopecia alopecia alopecia alopecia alopecia alopecia alopecia alopecia alopecia alopecia alopecia alopecia alopecia alopecia alopecia alopecia alopecia alopecia alopecia alopecia alopecia alopecia alopecia alopecia alopecia alopecia alopecia alopecia alopecia alopecia alopecia alopecia alopecia alopecia alopecia alopecia alopecia alopecia alopecia alopecia alopecia alopecia alopecia 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