Cytarabine Injection

For Intravenous, Intrathecal and Subcutaneous Use Only

WARNING

Only physicians experienced in cancer chemotherapy should use Cytarabine Injection. For induction therapy patients should be treated in a facility with laboratory and supportive resources sufficient to monitor drug tolerance and protect and maintain a patient compromised by drug toxicity. The main toxic effect of cytarabine injection is bone marrow suppression with leukopenia, thrombocytopenia and anemia. Less serious toxicity includes nausea, vomiting, diarrhea and abdominal pain, oral ulceration, and hepatic dysfunction. 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 judgement or beginning treatment, the physician should be familiar with the following text.

DESCRIPTION

Cytarabine Injection, an antineoplastic, is a sterile solution of cytarabine for intravenous, intrathecal or subcutaneous administration. Each mL contains 20 mg Cytarabine in 100 mg (20 mg/mL) single dose vial and 100 mg Cytarabine in 2 g (100 mg/mL) single dose vial.

Cytarabine Injection 100 mg/5 mL is a sterile solution for intravenous, intrathecal or subcutaneous administration. Each mL contains 20 mg Cytarabine, USP, and the following inactive ingredients: sodium chloride 6.8 mg and Water for Injection q.s. When necessary the pH is adjusted with hydrochloric acid and/or sodium hydroxide to a pH of 7.4. Each vial contains approximately 0.58 mEq sodium.

Cytarabine Injection 2 g/20 mL is a sterile solution for intravenous, intrathecal or subcutaneous administration. Each mL contains 100 mg Cytarabine, USP, 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.

Cytarabine is chemically 1-ß-D-Arabinofuranosylcytosine. The structural formula is:

\[
\text{Cytarabine (Cytarabine Injection)}
\]

Cytarabine is a colorless, 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-phase to the G2-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 chromatid 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.

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 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.

Human Pharmacology

Cytarabine is rapidly metabolized and is not effective orally; 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-ß-D-arabinofuranosyluracil (ara-U). Within 24 hours about 80 percent of the administered radioactivity can be recovered in the urine, approximately 90 percent of which is excreted as ara-U.

Relatively 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 60 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 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.

Immunosuppressive Action

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

INDICATIONS AND USAGE

Cytarabine Injection in combination with other approved anti-cancer 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 acute lymphocytic leukemia and the blast phase of chronic myelocytic leukemia. Intrathecal administration of Cytarabine Injection (preservative free preparations only) is indicated in the prophylaxis and treatment of meningeal leukemia.

CONTRAINDICATIONS

Cytarabine 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 induction therapy, should have leukocyte 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 that resulted in acute cardiopulmonary arrest and required resuscitation has been reported. This occurred immediately after the intravenous administration of cytarabine injection.

Severe and at times fatal CNS, GI and pulmonary toxicity (different from that seen with conventional therapy regimens of cytarabine injection) has been reported following some experimental dose schedules for cytarabine injection. 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 peptic ulcers and stomatitis leading to perforations; 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
Cytarabine Injection

Like other cytotoxic drugs, Cytarabine Injection 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 Injection by continuous infusion and in patients being treated with Cytarabine Injection who have had prior treatment with L-asparaginase.

2. Information for patient
Not applicable.

3. Laboratory tests
See General Precautions.

4. Drug Interactions
Reversible decreases in steady-state plasma digoxin concentrations and renal glycoside excretion were observed in patients receiving beta-acetyldigoxin and chemotherapy regimens containing cyclophosphamide, vincristine and prednisone with or without cytarabine injection or procarbazine.

Steady-state 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 K. pneumoniae strains. 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 re-evaluation of antibacterial therapy.

Clinical evidence in one patient showed possible inhibition of fluorouracil efficacy during therapy with cytarabine injection. This may be due to potential competitive inhibition of its uptake.

5. Carcinogenesis, mutagenesis, impairment of fertility
Extensive chromosomal damage, including 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.

7. Labor and delivery
Not applicable.

8. 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.

ADVERSE REACTIONS

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

Following 5-day constant infusions or acute injections of 50 mg/m² to 600 mg/m², white cell depression follows a biphasic course. Regardless of initial count, dosage level, or schedule, there is an initial fall starting the first 24 hours with a nadir at days 7-9. This is followed by a brief rise which peaks around the twelfth day. A second and deeper fall reaches nadir at days 15-24. Then there is 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. Thereupon, a second rise occurs with a peak at 21 days.

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PRECAUTIONS

1. General Precautions
Patients receiving Cytarabine Injection 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 has resulted in a platelet count under 50,000 or a polymorphonuclear 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 too quickly, patients are frequently nauseated and may vomit for several hours post-injection. This problem tends to be less severe when the drug is infused.

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

Periodic checks of bone marrow, liver and kidney functions should be performed in patients receiving cytarabine injection.

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Infectious Complications

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

The Cytarabine (Ara-C) Syndrome

A cytarabine syndrome has been described by Castleberry. It is characterized by fever, myalgia, bone pain, occasionally chest pain, maculopapular rash, conjunctivitis and malaise. It usually occurs 6-12 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 Injection.

Most Frequent Adverse Reactions

- anemia (oral and anal inflammation)
- rash (oral and anal inflammation)
- neutropenia
- renal dysfunction
- skin ulceration
- vomiting
- diarrhea
- fever

Nausea and vomiting are most frequent following rapid intravenous injection.

Less Frequent Adverse Reactions

- sepsis
- pneumonia
- cellulitis at injection site
- skin ulceration
- urinary retention
- renal dysfunction
- neutritis
- peripheral neuropathy
- paraplegia
- jaundice

Experimental Doses

Severe and at times fatal CNS, GI and pulmonary toxicity (different from that seen with conventional therapy regimens of cytarabine injection) has been reported following some experimental dose schedules of cytarabine injection. 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 pneumatoses caused by anti-leukemic therapy. 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.

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.

OVERDOSAGE

There is no antidote for overdosage of Cytarabine Injection. 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 as 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 infusional 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 anti-cancer drugs is 100 mg/m²/day by continuous IV infusion (Days 1-7) or 100 mg/m² IV every 12 hours (Days 1-7).

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.

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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 ultraviolet assay 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 98 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.
HANDLING AND DISPOSAL
Procedures for proper handling and disposal of anti-cancer drugs should be considered. Several guidelines on this subject have been published. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

HOW SUPPLIED
Cytarabine Injection is available as follows:
100 mg/5 mL in a single dose flip top vial (cool green cap) packaged in a carton of 5. NDC No.: 61703-305-38
2 g/20 mL in a single dose flip top vial (green cap) packaged individually. NDC No.: 61703-319-22

STORAGE CONDITIONS
Protect from light. Retain in carton until time of use.
Store the product at controlled room temperature 15° to 30°C (59° to 86°F).

REFERENCES

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