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 to 600 mg/m^2, 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 to 9. This is followed by a brief rise which peaks around day 12. A second and deeper fall reaches nadir at days 15 to 24. Then there is a rapid rise to above baseline in the next 10 days. Platelet depression is noticeable at day 5 with a peak depression occurring between days 12 to 15. Thereupon, a rapid rise to above baseline occurs in the next 10 days.

Infectious Complications: Infection - Viral, bacterial, fungal, parasitic, or saprophytic infections, in any location in the body may be associated with the use of cytarabine 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 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	hepatic dysfunction
nausea	fever
vomiting	rash
diarrhea	thrombophlebitis
oral and anal inflammation or ulceration	bleeding (all sites)

Nausea and vomiting are most frequent following rapid intravenous injection.

Less Frequent Adverse Reactions

sepsis	bowel necrosis
pneumonia	abdominal pain
cellulitis at injection site	freckling jaundice
skin ulceration	conjunctivitis (may occur with rash)
urinary retention	dizziness
renal dysfunction	alopecia
neuritis	anaphylaxis (See
neural toxicity	**"WARNINGS"** Section)
sore throat	allergic edema
esophageal ulceration	pruritus
esophagitis	shortness of breath
chest pain	urticaria
pericarditis	headache
pancreatitis	

Experimental Doses: 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 cytarabine treatment programs. If 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 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/m^2) with and without other chemotherapeutic agents (meta-AMSA, daunorubicin, etoposide) at various dose regimens 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.

OVERDOSAGE

There is no antidote for cytarabine overdosage. Doses of 4.5 g/m^2 by intravenous infusion over 1 hour every 12 hours for 12 doses has caused an unacceptable increase in irreversible CNS toxicity and death.

Single doses as high as 3 g/m^2 have been administered by rapid intravenous infusion without apparent toxicity.

DOSAGE AND ADMINISTRATION

Cytarabine is not active orally. The schedule and method of administration varies with the program of therapy to be used. Cytarabine may be given by intravenous infusion or injection, subcutaneously, or intrathecally. 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/m^2/day by continuous IV infusion (days 1 to 7) or 100 mg/m^2 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 has been used intrathecally in acute leukemia in doses ranging from 5 to 75 mg/m^2 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/m^2 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.

If used intrathecally, do not use a diluent containing benzyl alcohol. Many clinicians reconstitute with autologous spinal fluid or preservative-free 0.9% Sodium Chloride Injection USP and use immediately.

Cytarabine given intrathecally may cause systemic toxicity and careful monitoring of the hemopoietic 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 five 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.

When cytarabine 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 is left to the discretion of the treating physician.

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

The 100 mg vial may be reconstituted for intravenous and subcutaneous use with 5 mL Bacteriostatic Water for Injection USP with benzyl alcohol. The resulting solution contains 20 mg of cytarabine per mL. (Do not use Bacteriostatic Water for Injection USP with benzyl alcohol as a diluent for intrathecal use. See **"WARNINGS"** Section.)

The 500 mg vial may be reconstituted for intravenous and subcutaneous use with 10 mL Bacteriostatic Water for Injection USP with benzyl alcohol. The resulting solution contains 50 mg of cytarabine per mL. (Do not use Bacteriostatic Water for Injection USP with benzyl alcohol as a diluent for intrathecal use. See **"WARNINGS"** Section.)

The 1 g vial may be reconstituted for intravenous and subcutaneous use with 10 mL Bacteriostatic Water for Injection USP with benzyl alcohol. The resulting solution contains 100 mg of cytarabine per mL. (Do not use Bacteriostatic Water for Injection USP with benzyl alcohol as a diluent for intrathecal use. See **"WARNINGS"** Section.)

The 2 g vial may be reconstituted for intravenous and subcutaneous use with 20 mL Bacteriostatic Water for Injection USP with benzyl alcohol. The resulting solution contains 100 mg of cytarabine per mL. (Do not use Bacteriostatic Water for Injection USP with benzyl alcohol as a diluent for intrathecal use. See **"WARNINGS"** Section.)

If used intrathecally many clinicians reconstitute with preservative-free 0.9% Sodium Chloride Injection USP and use immediately.

The pH of the reconstituted solutions is about 5. Solutions reconstituted with Bacteriostatic Water for Injection USP with benzyl alcohol may be stored at controlled room temperature, 15° to 30°C (59° to 86°F), for 48 hours. Discard any solutions in which a slight haze develops.

Solutions reconstituted without a preservative should be used immediately.

NOTE: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Chemical Stability in Infusion Solutions: Chemical stability studies were performed by HPLC on cytarabine infusion solutions. These studies showed that when the reconstituted cytarabine was added to Water for Injection USP, 5% Dextrose Injection USP or 0.9% Sodium Chloride Injection USP, 93 to 99 percent of the cytarabine was present after 192 hours storage at room temperature. This chemical stability information in no way indicates that it would be acceptable practice to infuse a cytarabine admixture well after the preparation time. Good professional practice suggests that administration of compounded admixtures should be as soon after preparation as feasible.

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

Cytarabine for Injection USP is supplied as follows:

NDC 55390-131-10	100 mg boxed vial; pack of 10
NDC 55390-132-10	500 mg boxed vial; pack of 10
NDC 55390-133-01	1 g boxed vial
NDC 55390-134-01	2 g boxed vial

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

REFERENCES

1. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs. NIH Publication No. 83-2621. Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402
2. AMA Council Report. Guidelines for Handling Parenteral Antineoplastics, *JAMA*, March 15, 1985.
3. National Study Commission on Cytotoxic Exposure — Recommendations for Handling Cytotoxic Agents, Louis P. Jeffrey, Sc.D., Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Ave., Boston, Massachusetts 02115.
4. Clinical Oncological Society of Australia: Guidelines and Recommendations for Safe Handling of Antineoplastic Agents. *Med J Aust* 1:426-428, 1983.
5. Jones RB, *et al:* Safe Handling of Chemotherapeutic Agents: A report from the Mount Sinai Medical Center, *CA — A Cancer Journal for Clinicians* Sept/Oct, 258-263, 1983.
6. American Society of Hospital Pharmacists Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs. *Am J Hosp Pharm* 47:1033-1049, 1990.
7. Controlling Occupational Exposure to Hazardous Drugs. (OSHA Work-Practice Guidelines), *Am J Hosp Pharm*, 53:1669-1685, 1996.

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