CYTOSAR
CYTARABINE
Powder for solution for injection

NAME OF THE MEDICINAL PRODUCT

Cytosar

QUALITATIVE AND QUANTITATIVE COMPOSITION

Powder freeze dried and diluent for solution for injection, containing cytarabine 100 mg and 500 mg.

PHARMACEUTICAL FORM

Powder freeze dried and diluent for solution, for injection

INDICATIONS AND CLINICAL USE

Cytosar (cytarabine) is indicated primarily for induction and maintenance of remission in acute leukemia in both adults and children.

It has been found useful in the treatment of acute myelocytic leukemia, chronic myelocytic leukemia (blast phase), acute lymphocytic leukemia and erythroleukemia. Cytosar may be used alone or in combination with other antineoplastic agents; the best results are obtained with combination therapy.

Children with non-Hodgkin's lymphoma have benefited from a combination drug program (LSA_2L_2) that included Cytosar.

Cytosar has been used intrathecally in newly diagnosed children with acute lymphocytic leukemia as well as in the treatment of meningeal leukemia.

Cytosar, in high dose 2-3 g/m^2 as an i.v. infusion over 1-3 hours given every 12 hours for 2-6 days with or without additional cancer chemotherapeutic agents, has been shown to be effective in the treatment of poor-risk leukemia, refractory leukemia, and relapsed acute leukemia.

Remissions induced by Cytosar not followed by maintenance treatment have been brief.

CONTRAINDICATIONS

Cytosar (cytarabine) is contraindicated in those patients who are hypersensitive to the drug. Anaphylactic reactions have occurred with Cytosar treatment (see WARNINGS AND PRECAUTIONS, Sensitivity/Resistance).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Cytosar (cytarabine) should be prescribed only by physicians experienced with cancer therapy drugs. Patients should be monitored and blood counts as well as renal and hepatic function tests should be performed regularly (see WARNINGS AND PRECAUTIONS, Hematologic, Hepatic/Biliary/Pancreatic, Renal, Monitoring and Laboratory Tests and OVERDOSAGE).

Do not use a diluent that contains benzyl alcohol when giving to premature or low birth weight infants as benzyl alcohol has been associated with the "gasping syndrome" (see WARNINGS AND PRECAUTIONS, General and Special Populations, Pediatrics). Do not use a diluent that contains benzyl alcohol for high dose therapy or when using intrathecally (see ADVERSE REACTIONS, High Dose Therapy and DOSAGE AND ADMINISTRATION, Reconstitution, Lyophilized Powder).

The following are clinically significant adverse events:

- Cardiomyopathy with subsequent death (see WARNINGS AND PRECAUTIONS, Cardiovascular and ADVERSE REACTIONS, High Dose Therapy).
- GI toxicity, at times fatal (see WARNINGS AND PRECAUTIONS, Gastrointestinal and ADVERSE REACTIONS, High Dose Therapy).
- Acute pancreatitis (see WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic).
- CNS toxicity, severe neurological adverse reactions, paraplegia, necrotizing leukoencephalopathy and spinal cord toxicity. Patients with impaired hepatic or renal function may be at increased risk after high dose Cytosar (see WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic, Neurologic and Renal; ADVERSE REACTIONS, High Dose Therapy and Intrathecal Therapy; DRUG INTERACTIONS, Serious Interactions; DOSAGE AND ADMINISTRATION, Meningeal Leukemia - Intrathecal Use, OVERDOSAGE, and ACTION AND CLINICAL PHARMACOLOGY).
- Infection (see WARNINGS AND PRECAUTIONS, Immune and ADVERSE REACTIONS, Infections and Infestations).
- Pulmonary toxicity, adult respiratory distress syndrome and pulmonary edema (see WARNINGS AND PRECAUTIONS, Respiratory and ADVERSE REACTIONS, High Dose Therapy).
- Myelosuppression (see WARNINGS AND PRECAUTIONS, Hematologic; ADVERSE REACTIONS, Blood and Lymphatic System Disorders and OVERDOSAGE).

General

Before instituting a programme of combined therapy, the physician should be familiar with the literature, adverse reactions, warnings and precautions, and contraindications applicable to all the drugs in the programme (see DOSAGE AND ADMINISTRATION, Combined Chemotherapy).

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 Cytosar is bone marrow suppression with leukopenia, thrombocytopenia and anemia. Less serious toxicity includes nausea, vomiting, diarrhea and abdominal pain, oral ulceration, and hepatic dysfunction (see ADVERSE REACTIONS).

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

When large intravenous doses are given 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.

Bacteriostatic water, one of the diluents recommended for reconstitution of Cytosar, contains benzyl alcohol (see DOSAGE AND ADMINISTRATION, Reconstitution, Lyophilized Powder). Benzyl alcohol has been reported to be associated with a fatal "Gasping Syndrome" in pediatric patients. As premature and low birth weight infants may be at increased risk of developing this toxicity, they should not be given cytarabine reconstituted with a diluent containing benzyl alcohol (see WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics).

Carcinogenesis and Mutagenesis
Extensive chromosomal damage, including chromatoid breaks have been produced by cytarabine and malignant transformation of rodent cells in culture has been reported (see DETAILED PHARMACOLOGY).

Cardiovascular
High dose schedules: An increase in cardiomyopathy with subsequent death has been reported following experimental high dose Cytosar and cyclophosphamide therapy when used for bone marrow transplant preparation. This may be schedule dependent (see also DRUG INTERACTIONS).

Gastrointestinal
Abdominal tenderness (peritonitis) and typhlitis with concurrent neutropenia and thrombocytopenia have been reported in patients treated with conventional doses of cytarabine in combination with other drugs. Patients have responded to non-operative medical management.

High dose schedule: Severe and at times fatal, GI toxicity (different from that seen with conventional therapy regimens of Cytosar) has been reported following high dose (2-3 g/m^2) schedules of Cytosar. These reactions include severe gastrointestinal ulceration, including pneumatosis cystoides intestinalis, leading to peritonitis, bowel necrosis; and necrotizing colitis.

Genitourinary
Tumor Lysis Syndrome: Like other cytotoxic drugs, Cytosar 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 measurements as might be necessary to control this problem.

Hematologic
Cytosar (cytarabine) is a potent bone marrow suppressant; the severity depends on the dose of the drug and schedule of administration. 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). Periodic checks of bone marrow should be performed in patients receiving Cytosar.

Hepatic/Biliary/Pancreatic
The human liver may detoxify a substantial fraction of an administered cytarabine dose. In particular, patients with hepatic function impairment may have a higher likelihood of CNS toxicity after high dose treatment with Cytosar. Use the drug with caution and at reduced dose in patients whose liver function is poor.

Periodic checks of liver function should be performed in patients receiving Cytosar.

Pancreatitis: Acute pancreatitis has been reported to occur in patients being treated with Cytosar in combination with other drugs.

High dose schedules: Other reactions have been reported following high dose (2-3 g/m^2) schedules of Cytosar and include sepsis and liver abscess, and liver damage with increased hyperbilirubinemia.

Immune
Immunosuppressant Effects/Increased Susceptibility to Infections: Administration of live or live-attenuated vaccines in patients immunocompromised by chemotherapeutic agents, including cytarabine, may result in serious or fatal infections. Vaccination with a live vaccine should be avoided in patients receiving cytarabine. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

Neurologic
High dose schedules: Severe and at times fatal, CNS toxicity (different from that seen with conventional therapy regimens of Cytosar) has been reported following high dose (2-3 g/m^2) schedules of Cytosar. These reactions include cerebral and cerebellar dysfunction including personality changes, somnolence, convulsion and coma, usually reversible.

Delayed progressive ascending paralysis resulting in death has been reported in children with AML following intrathecal and intravenous cytarabine at conventional doses in combination with other drugs.

Cases of severe neurological adverse reactions that ranged from headache to paralysis, coma and stroke-like episodes have been reported mostly in pediatric patients given intravenous cytarabine in combination with intrathecal methotrexate.

Ophthalmologic
High dose schedules: The following reactions have been reported following high dose (2-3 g/m^2) schedules of Cytosar: reversible corneal toxicity and hemorrhagic conjunctivitis, which may be prevented or diminished by prophylaxis with a local corticosteroid eye drop.

Renal
Patients with renal function impairment may have a higher likelihood of CNS toxicity after high dose treatment with Cytosar. Periodic checks of kidney function should be performed in patients receiving Cytosar.

Respiratory
High dose schedules: Severe and sometimes fatal pulmonary toxicity, adult respiratory distress syndrome and pulmonary edema have occurred following high dose schedules with cytarabine therapy. A syndrome of sudden respiratory distress, rapidly progressing to pulmonary edema and radiographically pronounced cardiomegaly has been reported following experimental high dose Cytosar therapy used for the treatment of relapsed leukemia.

Sensitivity/Resistance
Anaphylactic reactions have occurred with cytarabine treatment. Anaphylaxis that resulted in acute cardiopulmonary arrest and required resuscitation has been reported. This occurred immediately after the intravenous administration of Cytosar.

Sexual Function/Reproduction
Male Fertility: Cytosar may present in the semen. Male patients who are not surgically sterile must agree to use effective contraception during treatment with Cytosar to prevent pregnancy in female partners (see WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Women and TOXICOLOGY).

Skin
Palmar plantar erythrodysaesthesia: Palmar plantar erythrodysaesthesia (PPE) has occurred with cytarabine treatment in adults and children. Severe cytarabine associated PPE that resulted in treatment discontinuation has been reported.

High dose schedules: Rarely, severe skin rash, leading to desquamation has been reported. Complete alopecia is more commonly seen with high dose therapy than with standard Cytosar treatment programs.

Special Populations

Pregnant Women
Cytarabine is embryotoxic and teratogenic and produced peri- and postnatal toxicity

in various species. Sperm head abnormalities were observed following cytarabine treatment in mice (see TOXICOLOGY).

There are no studies on the use of cytarabine in pregnant women. Use of this drug in women who are or who may become pregnant should be undertaken only after due consideration of potential benefit and potential hazard to both mother and child. Women of childbearing potential should be advised to avoid becoming pregnant (see also WARNINGS AND PRECAUTIONS, Sexual Function/Reproduction).

Normal infants have been born to mothers exposed to cytarabine during pregnancy (alone or in combination with other drugs); some of these infants were premature or of low birth weight. Some of the normal infants were followed up at ages ranging from six weeks to seven years following exposure, and showed no abnormalities. One apparently normal infant died at 80 days of gastroenteritis.

Congenital abnormalities have been reported, particularly when the fetus has been exposed to systemic therapy with cytarabine during the first trimester. These include upper and lower distal limb defects, and extremity and ear deformities.

Reports of pancytopenia, leukopenia, anemia, thrombocytopenia, electrolyte abnormalities, transient oesinophilia, increased IgM levels and hyperpyrexia, sepsis and death have occurred during the neonatal period to infants exposed to cytarabine *in utero*. Some of these infants were also premature.

Therapeutic abortions have been done in pregnant women on cytarabine. Normal fetuses have been reported while other reported fetal effects included enlarged spleen and 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 becomes pregnant while on Cytosar should be apprised of the potential risk to the fetus and the advisability of pregnancy continuation. 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.

Bacteriostatic water, one of the diluents recommended for reconstitution of Cytosar, contains benzyl alcohol. Benzyl alcohol can cross the placenta (see WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics).

Nursing Women

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.

Pediatrics

The safety of this drug for use in infants (under 1 year of age) is not established.

Gasping Syndrome: Cytarabine should not be given to premature and low birth weight infants when using a diluent that contains benzyl alcohol. The preservative benzyl alcohol has been associated with serious adverse events, including the “gasping syndrome”, and death in pediatric patients. Symptoms of gasping syndrome may include metabolic acidosis, seizure, bradycardia, gasping respiration and cardiovascular collapse. Although normal therapeutic doses of this product ordinarily deliver amounts of benzyl alcohol that are substantially lower than those reported in association with the “gasping syndrome”, the minimum amount of benzyl alcohol at which toxicity may occur is not known. The risk of benzyl alcohol toxicity depends on the quantity administered and the hepatic capacity to detoxify the chemical. Premature and low-birth weight infants may be more likely to develop toxicity. If cytarabine is used in high dose or intrathecal therapy, do not use a diluent containing benzyl alcohol. The preservative-free 0.9% sodium chloride can be used for reconstitution (see also SERIOUS WARNINGS AND PRECAUTIONS).

See also WARNINGS AND PRECAUTIONS, Neurologic and Skin.

Monitoring and Laboratory Tests
Patients receiving Cytosar (cytarabine) must be monitored closely. Frequent platelet and leukocyte 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/mm^3. 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 of 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.

ADVERSE REACTIONS

Adverse Drug Reaction Overview
The following listing is based on adverse events reported in clinical trials and/or spontaneous adverse event reports from post-marketing experience. When a frequency cannot be estimated from the available data it is classified as “not known”.

Blood and Lymphatic System Disorders
Because Cytosar (cytarabine) is a bone marrow suppressant, anemia, leukopenia, thrombocytopenia, megaloblastosis, and reduced reticulocytes can be expected as a result of its administration. The severity of these reactions is dose and schedule dependent. Cellular changes in the morphology of bone marrows and peripheral smears can be expected.

Following 5-day constant infusions or acute injections of 50 mg/m^2 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 the twelfth day. 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 5 days with a peak depression occurring between days 12 to 15. Thereupon, a rapid rise to above baseline occurs in the next 10 days.

Infections and Infestations
Viral, bacterial, fungal, parasitic, or saprophytic infections, in any location on the body, may be associated with the use of Cytosar 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.

Musculoskeletal and Connective Tissue Disorders

The Cytarabine Syndrome
A cytarabine syndrome has been described by Castleberry *et al.* 1981. 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 Cytosar.

Other Adverse Reactions

Conventional Dose Therapy
Nausea and vomiting are most frequent following rapid intravenous injection.

The reported adverse reactions are listed below by MedDRA System Organ Class and by frequency.

ADR frequencies are based on CIOMS convention: Very common (>10%), Common (>1%, ≤10%), Uncommon (>0.1%, ≤1%), Rare (>0.01%, ≤0.1%), and Frequency not known (cannot be estimated from available data).

Table 1 – Frequencies of Adverse Reactions with Cytosar conventional dose therapy

Blood and Lymphatic System Disorders:	
Very common	Bone marrow failure, thrombocytopenia, anaemia, anaemia megaloblastic, leukopenia, reticulocyte count decreased
Frequency not known	Bleeding (all sites)
Cardiac Disorders:	
Frequency not known	Pericarditis
Eye Disorders:	
Frequency not known	Conjunctivitis[a]
Gastrointestinal Disorders:	
Very common	Stomatitis, mouth ulceration, anal ulcer, anal inflammation, diarrhoea, vomiting, nausea, abdominal pain
Frequency not known	Bowel necrosis, pancreatitis, oesophageal ulcer, oesophagitis
General Disorders and Administration Site Conditions:	
Very common	Pyrexia

Frequency not known	Chest pain, injection site reaction[b]
Hepatobiliary Disorders:	
Very common	Hepatic function abnormal
Frequency not known	Jaundice
Immune System Disorders:	
Frequency not known	Anaphylactic reaction, allergic oedema
Infections and Infestations:	
Very common	Sepsis, pneumonia, infection[c]
Frequency not known	Injection site cellulitis
Investigations:	
Very common	Biopsy bone marrow abnormal, blood smear test abnormal
Metabolism and Nutrition Disorders:	
Frequency not known	Decreased appetite
Musculoskeletal, Connective Tissue and Bone Disorders:	
Very common	Cytarabine syndrome
Nervous System Disorders:	
Frequency not known	Neurotoxicity, neuritis, dizziness, headache
Renal and Urinary Disorders:	
Frequency not known	Renal impairment, urinary retention
Respiratory, Thoracic and Mediastinal Disorders:	
Frequency not known	Dyspnoea, oropharyngeal pain
Skin and Subcutaneous Tissue Disorders:	
Very common	Alopecia, rash
Common	Skin ulcer
Frequency not known	Palmar-plantar erythrodysaesthesia syndrome, urticaria, pruritus, freckling
Vascular Disorders:	
Frequency not known	Thrombophlebitis

[a] May occur with rash and may be hemorrhagic with high dose therapy
[b] Pain and inflammation at subcutaneous injection site
[c] May be mild, but can be severe and at times fatal

High Dose Therapy

Severe and at times fatal CNS, GI and pulmonary toxicity (different from that seen with conventional therapy regimens of Cytosar) has been reported following high dose schedules (2.0 g to 3.0 g/m^2 given every 12 hours for 12 doses).

The reported adverse reactions are listed below by MedDRA System Organ Class and by frequency.

ADR frequencies are based on CIOMS convention: Very common (>10%), Common (>1%, ≤10%), Uncommon (>0.1%, ≤1%), Rare (>0.01%, ≤0.1%), and Frequency not known (cannot be estimated from available data).

Table 2 – Frequencies of Adverse Reactions with Cytosar High Dose Therapy

Cardiac Disorders:	
Frequency not known	Cardiomyopathy[a]
Eye Disorders:	

Very common	Corneal disorder
Frequency not known	Hemorrhagic conjunctivitis[b]
Gastrointestinal Disorders:	
Common	Necrotising colitis
Frequency not known	Gastrointestinal necrosis, gastrointestinal ulcer, pneumatosis intestinalis, peritonitis
Hepatobiliary Disorders:	
Frequency not known	Liver injury, hyperbilirubinaemia
Infections and Infestations:	
Very common	Sepsis
Frequency not known	Liver abscess
Nervous System Disorders:	
Very common	Cerebral disorder, cerebellar disorder, somnolence
Frequency not known	Coma, convulsion, peripheral motor neuropathy, peripheral sensory neuropathy
Psychiatric Disorders:	
Frequency not known	Personality change[c]
Respiratory, Thoracic and Mediastinal Disorders:	
Very common	Acute respiratory distress syndrome, pulmonary oedema
Skin and Subcutaneous Tissue Disorders:	
Common	Skin exfoliation

[a] With subsequent death
[b] May be prevented or diminished by prophylaxis with a local corticosteroid eyedrop
[c] Personality change was reported in association with cerebral and cerebellar dysfunction.

Peripheral motor and sensory neuropathies after consolidation with high dose Cytosar, daunorubicin, and asparaginase have occurred in adult patients with acute non lymphocytic leukemia. Patients treated with high dose Cytosar should be observed for neuropathy since dose schedule alterations may be needed to avoid irreversible neurologic disorders.

Corneal toxicity consisting of ocular pain, tearing, foreign-body sensation, photophobia and blurred vision has been reported.

Rarely, severe skin rash, leading to desquamation has been reported. Complete alopecia is more commonly seen with high dose therapy than with standard Cytosar treatment programs.

If high dose therapy is used, do not use a diluent containing benzyl alcohol.

Intermediate Dose Therapy
A diffuse interstitial pneumonitis without clear cause that may have been related to Cytosar was reported in patients treated with experimental intermediate doses of Cytosar (1 gm/m^2) with and without other chemotherapeutic agents (meta-AMSA, daunorubicin, VP-16).

Intrathecal Therapy
Cytosar 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 with or without convulsion has been reported; in some cases, patients had also been treated with intrathecal methotrexate and/or 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 Cytosar. When Cytosar 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 Cytosar is left to the discretion of the treating physician.

DRUG INTERACTIONS

Serious Drug Interactions

- **Methotrexate:** Intravenous cytarabine given concomitantly with intrathecal methotrexate may increase the risk of severe neurological adverse reactions such as headache, paralysis, coma and stroke-like episodes.

Drug-Drug Interactions

Digoxin: 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 or procarbazine. Steady-state plasma digitoxin 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 digitoxin for such patients may be considered as an alternative.

Gentamicin: 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.

Fluorocytosine: Clinical evidence showed possible inhibition of fluorocytosine efficacy therapy with cytarabine. This may be due to potential competitive inhibition of its uptake.

Experimental high dose Cytosar and cyclophosphamide therapy: An increase in cardiomyopathy with subsequent death has been reported when used for bone marrow transplant preparation. This may be schedule dependent (see WARNINGS AND PRECAUTIONS, Cardiovascular).

Drug-Food Interaction

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal product have not been established.

Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions

Interactions associated with lifestyle have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Clinical experience accumulated to date suggests that success with Cytosar is dependent more on adeptness in modifying day-to-day dosage to obtain maximum leukemic cell kill with tolerable toxicity than on the basic treatment schedule chosen at the outset of therapy. Toxicity necessitating dosage alteration almost always occurs.

In many chemotherapeutic programs, Cytosar is used in combination with other cytotoxic drugs. The addition of these cytotoxic drugs has necessitated changes and dose alterations. The dosage schedules for combination therapy outlined below have been reported in the literature (see REFERENCES).

Recommended Dose and Dosage Adjustment

Acute myelocytic leukemia - induction remission: adults

Cytosar 200 mg/m^2 daily by continuous infusion for 5 days (120 hours) - total dose 1000 mg/m^2. This course is repeated approximately every 2 weeks. Modifications must be made based on hematologic response.

Acute myelocytic leukemia - maintenance: adults

Maintenance programs are modifications of induction programs and, in general, use similar schedules of drug therapy as were used during induction. Most programs have a greater time spacing between courses of therapy during remission maintenance.

Acute myelocytic leukemia - induction and maintenance in children

Numerous studies have shown that childhood AML responds better than adult AML given similar regimens. Where the adult dosage is stated in terms of body weight or surface area, the children's dosage may be calculated on the same basis. When specified amounts of a drug are indicated for the adult dosage, these should be adjusted for children on the basis of such factors as age, body weight or body surface area.

Acute myelocytic leukemia – adults and children

The following tables outline the results of treatment with Cytosar alone and in combination with other chemotherapeutic agents, in the treatment of acute myelocytic leukemia in adults and children.

The treatment regimens outlined in the tables should not be compared for efficacy. These were independent studies with a number of variables involved, such as patient population, duration of disease, and previous treatment.

The responsiveness and course of childhood acute myelocytic leukemia (AML) appear to be different from that in adults. Numerous studies show response rates to be higher in children than in adults with similar treatment schedules. Experience indicates that at least with induction and initial drug responsiveness, childhood AML appears to be more similar to childhood acute lymphocytic leukemia (ALL) than to its adult variant.

Patients with hepatic impairment: Cytarabine and dose adjustment has not been studied in individuals with hepatic impairment (see also WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic).

Patients with renal impairment: Cytarabine and dose adjustment has not been studied in individuals with renal impairment (see also WARNINGS AND PRECAUTIONS, Renal).

TABLE I
Acute Myelocytic Leukemia - Remission Induction: Adults

Drug Dosage Schedule*		**No. of Patients Evaluated**	**Complete Remissions**	**Investigators**
Cytosar Single-Dose Therapy	(Infusion)			
	10 mg/m^2 12 hrs/day	12	2 (17%)	Ellison (1968)
	30 mg/m^2 12 hrs/day	41	10 (24%)	
	10 mg/m^2 24 hrs/day	9	2 (22%)	
	30 mg/m^2 24 hrs/day	36	2 (6%)	
	(Infusion) 200 mg/m^2 24 hrs/5 days	36	9 (25%)	Bodey (1969)
	10 mg/m^2 i.v. injection initially, then infusions of 30 mg/m^2 per 12 hrs or 60 mg/m^2/day for 4 days	49	21 (43%)	Goodell (1970)
	(Infusion Therapy) 800 mg/m^2/2 days	53	12 (23%)	Southwest Oncology Group (1974)
	1000 mg/m^2/5 days	60	24 (40%)	
	100 mg/m^2/day 1 hr infusion	49	7 (14%)	Carey (1975)
	5-12.5 mg/kg/12 hr infusion following i.v. synchronizing dose**	5	5 (100%)	Lampkin (1976)
Combined Therapy	Cytosar - doxorubicin	41	30 (73%)	Preisler (1979)
	Cytosar - thioguanine daunorubicin	28	22 (79%)	Gale (1977)
	Cytosar - doxorubicin vincristine - prednisolone	35	23 (66%)	Weinstein (1980)
	Cytosar - daunorubicin thioguanine - prednisone vincristine	139	84 (60%)	Glucksberg (1981)

Drug Dosage Schedule*		No. of Patients Evaluated	Complete Remissions	Investigators
	Cytosar - daunorubicin	21	14 (67%)	Cassileth (1977)
High Dose Therapy	Cytosar	7	6 (86%)	Lister (1983)
	Cytosar	21	12 (57%)	Herzig (1983)
Cytosar	Cytosar	11	8 (73%)	Preisler (1983)
	Cytosar - doxorubicin	14	7 (50%)	Willemze (1982)
	Cytosar - asparaginase	13	9 (69%)	Capizzi (1983)

* Unless otherwise stated, all doses given until drug effect-modifications then based on hematologic reasons. See REFERENCES.
** Highly experimental - requires ability to study mitotic indices.

TABLE II
Acute Myelocytic Leukemia - Remission Induction: Children (21 and under)

Drug Therapy	No. of Patients Evaluated	Complete Remissions	Investigator
Cytosar (5-12.5 mg/kg following i.v. synchronizing dose**)	16	12 (75%)	Lampkin (1976)
Cytosar, vincristine, doxorubicin, prednisolone	48	35 (73%)	Weinstein (1980)
Cytosar, thioguanine, doxorubicin	11	8 (72%)	Hagbin (1975)
Cytosar, thioguanine	47	20 (43%)	Pizzo (1976)
Cytosar, cyclophosphamide	12	7 (58%)	Pizzo (1976)

** Highly experimental - requires ability to study mitotic indices.

Acute lymphocytic leukemia

In general, dosage schedules are similar to those used in acute myelocytic leukemia with some modification. Cytosar has been used in the treatment of acute lymphocytic leukemia in both adults and children. When Cytosar was used with other antineoplastic agents as part of a total therapy program, results were equal to or better than reported with such programs which did not include Cytosar. Used singly, or in combination with other agents, Cytosar has also been effective in treating patients who had relapsed on other therapy. Table III and IV summarize the results obtained in previously treated patients. Since these are independent studies with such variables as patient population, duration of disease and previous treatment, results shown should not be used for comparing the efficacy of the outlined treatment programs.

TABLE III
Acute Lymphocytic Leukemia - Remission Induction
Previously Treatment Patients
Adults and Children

Drug Therapy	No. of Patients Evaluated	Complete Remissions	Response	Investigator
Cytosar 3-5 mg/kg/day (IV injection)	43	2 (5%)	15 (35%)	Howard (1968)
Cytosar - asparaginase	9	8 (89%)	8 (89%)	McElwain (1969)
Cytosar - cyclophosphamide	11	7 (64%)	9 (82%)	Bodey 1970
Cytosar - prednisone	83	-	(49%)	Nesbitt (1970)

Drug Therapy	No. of Patients Evaluated	Complete Remissions	Response	Investigator
Cytosar 150-200 $mg/m^2/5$ days (infusion)	34	1 (3%)	4 (12%)	Wang (1970)
Cytosar - L - asparaginase - prednisone - vincristine - doxorubicin	91	72 (79%)	-	Klemperer (1978)
Cytosar - L - asparaginase - prednisone - vincristine - doxorubicin	55	42 (76%)	-	Klemperer (1978)
Cytosar - asparaginase	22	13 (59%)	15 (68%)	Ortaga (1972)
Cytosar - thioguanine	19	9 (47%)	9 (47%)	Bryan (1974)

TABLE IV

Drug Therapy		No. of Patients Evaluated	Complete Remissions	Investigator
High Dose Therapy	Cytosar	8	3 (38%)	Rohatinar (1983)
	Cytosar - doxorubicin	3	2 (67%)	Willemze (1982)
	Cytosar - asparaginase	10	3 (30%)	Capizzi (1983)

Non-Hodgkin's lymphoma in children
Cytosar has been used as part of multi-drug program (LSA_2L_2) to treat non-Hodgkin's lymphoma in children. See Appendix A for complete dosage schedule.

High Dose Chemotherapy
Before instituting a program of high dose chemotherapy, the physician should be familiar with the literature, adverse reactions, precautions, contraindications, and warnings applicable to all the drugs involved in the program.

Cytosar
Cytosar: 2 g/m^2 infused over 3 hours every 12 hours x 12 doses (Days 1-6).

Cytosar
Cytosar: 3 g/m^2 infused over 1 hour every 12 hours x 12 doses (Days 1-6).

Cytosar
Cytosar: 3 g/m^2 infused over 75 minutes every 12 hours x 12 doses (Days 1-6).

Cytosar - doxorubicin
Cytosar: 3 g/m^2 infused over 2 hours every 12 hours x 12 doses (Days 1-6).
Doxorubicin: 30 mg/m^2 i.v. on Days 6-7.

Cytosar - asparaginase
Cytosar: 3 g/m^2 infused over 3 hours at 0 hours, 12 hours, 24 hours, and 36 hours. At 42 hours, 6000 $units/m^2$ of asparaginase i.m. (Days 1-2); repeat same schedule Days 8-9.

Combined Chemotherapy
Before instituting a program of combined chemotherapy, the physician should be familiar with the literature, adverse reactions, precautions, contraindications, and

warnings applicable to all the drugs involved in the program.

Cytosar, doxorubicin
Cytosar: 100 mg/m^2/day, continuous i.v. infusion (Days 1-10).
Doxorubicin: 30 mg/m^2/day, i.v. infusion of 30 minutes (Days 1-3).

Additional (complete or modified) courses as necessary at 2-4 week intervals if leukemia is persistent.

Cytosar, thioguanine, daunorubicin
Cytosar: 100 mg/m^2, i.v. infusion over 30 minutes every 12 hours (Days 1-7).
Thioguanine: 100 mg/m^2, orally every 12 hours (Days 1-7).
Daunorubicin: 60 mg/m^2/day, i.v. infusion (Days 5-7).

Additional (complete or modified) courses as necessary at 2-4 week intervals if leukemia is persistent.

Cytosar, doxorubicin, vincristine, prednisone
Cytosar: 100 mg/m^2/day, continuous i.v. infusion (Days 1-7).
Doxorubicin: 30 mg/m^2/day, i.v. infusion (Days 1-3).
Vincristine: 1.5 mg/m^2/day, i.v. infusion (Days 1, 5).
Prednisolone: 40 mg/m^2/day, i.v. infusion every 12 hours (Days 1-5).

Additional (complete or modified) courses as necessary at 2-4 week intervals if leukemia is persistent.

Cytosar, daunorubicin, thioguanine, prednisone, vincristine
Cytosar: 100 mg/m^2/day, i.v. infusion (Days 1-10).
Daunorubicin: 70 mg/m^2/day, i.v. infusion (Days 1-3).
Thioguanine: 100 mg/m^2, orally every 12 hours (Days 1-7).
Prednisone: 40 mg/m^2/day, orally (Days 1-7).
Vincristine: 1 mg/m^2/day, i.v. infusion (Days 1, 7).

Additional (complete or modified) courses as necessary at 2-4 week intervals if leukemia is persistent.

Cytosar, daunorubicin
Cytosar: 100 mg/m^2/day, continuous i.v. infusion (Days 1-7).
Daunorubicin: 45 mg/m^2/day, i.v. push (Days 1-3).

Additional (complete or modified) courses as necessary at 2-4 week intervals if leukemia is persistent.

Meningeal Leukemia - Intrathecal Use
Cytosar has been used intrathecally in acute leukemia in doses ranging from 5 mg/m^2 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.

Cytosar has been used intrathecally with hydrocortisone sodium succinate and methotrexate, both as prophylaxis in newly diagnosed children with acute lymphocytic leukemia, as well as in the treatment of meningeal leukemia. Sullivan *et al.* has reported that prophylactic triple therapy has prevented late CNS disease and given overall cure and survival rates similar to those seen in patients in whom CNS radiation and intrathecal methotrexate was used as initial CNS prophylaxis. The dose of Cytosar was 30 mg/m^2, hydrocortisone sodium succinate 15 mg/m^2, and methotrexate 15 mg/m^2 (an absolute maximum single dose of 15 mg of methotrexate). The physician should be aware of this regimen and note that methotrexate dosage in pediatric patients is otherwise based on age rather than body surface area. Prescribers should consult related Product Leaflet for more information.

Prophylactic triple therapy following the successful treatment of the acute meningeal episode may be useful. The physician should familiarize himself with the current literature before instituting such a program.

Cytosar given intrathecally may cause systemic toxicity and careful monitoring of the hemopoietic system is indicated. Modification of the 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 Cytosar.

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

If used intrathecally, do not use a diluent containing benzyl alcohol. Reconstitute with preservative free saline and use immediately.

Dosage Modification

The dosage of Cytosar must be modified or suspended when signs of serious hematologic depression appear. In general, consider discontinuing the drug if the patient has less than 50,000 platelets or 1000 polymorphonuclear granulocytes/mm^3 in his peripheral blood. These guidelines may be modified depending on signs of toxicity in other systems and on the rapidity of fall in formed blood elements. Restart the drug when there are signs of marrow recovery and the above platelet and granulocyte levels have been attained. Withholding therapy until the patient's blood values are normal may result in escape of the patient's disease from control by the drug.

Hepatic Insufficiency: Use cytarabine with caution or possibly at reduced doses in patients whose liver function is poor (see also WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic).

Renal Insufficiency: Use cytarabine with caution or possibly at reduced doses in patients whose kidney function is poor (see also WARNINGS AND PRECAUTIONS, Renal)**.**

Administration
Cytosar is not active orally. The schedule and method of administration varies with the program of therapy to be used. Cytosar may be given by intravenous infusion, injection/subcutaneously or intrathecally. When preparing cytarabine for intravenous high dose therapy or intrathecal use, do not use diluents containing benzyl alcohol (see SERIOUS WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION, Reconstitution, Lyophilized Powder). It is recommended that Cytosar be reconstituted with preservative-free 0.9% sodium chloride for injection and used immediately.

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

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

Reconstitution

Characteristics of Reconstituted Solution from Lyophilized Powder:
- pH of reconstituted solution is approximately 5.
- Solutions reconstituted without a preservative should be used immediately.
- Solutions reconstituted with Bacteriostatic Water for Injection with Benzyl Alcohol 0.9% (for multi-dose use) may be stored at 30°C ± 2°C for 24 hours.
- Discard any solution in which a slight haze develops.

Reconstitution of Lyophilized Powder
Cytosar may be reconstituted with the diluents mentioned below and mixed with the compatible drugs mentioned in the **CHEMICAL STABILITY AND COMPATIBILITY** section. Compatibility must be assured before mixing with any other substance.

Cytosar may be reconstituted with the following diluents:
- 0.9% Sodium Chloride for Injection
- Dextrose 5% in Water
- Sterile Water for Injection
- Bacteriostatic Water for Injection

When reconstituted with a diluent, the following concentrations result:

Vial Size	Volume of Diluent to be added to Vial	Nominal Concentration
100 mg	5 mL	20 mg/mL
500 mg	10 mL	50 mg/mL

Solutions reconstituted without a preservative should be used immediately. Solutions reconstituted with Bacteriostatic Water for Injection with Benzyl Alcohol 0.9% may be stored at 30°C ± 2°C for 24 hours.

FOR INTRATHECAL USE: DO NOT USE DILUENT CONTAINING BENZYL ALCOHOL. RECONSTITUTE WITH PRESERVATIVE-FREE 0.9% SODIUM CHLORIDE FOR INJECTION. USE IMMEDIATELY.

FOR HIGH DOSE USE: DO NOT USE DILUENT CONTAINING BENZYL ALCOHOL.

OVERDOSAGE

There is no antidote for Cytosar (cytarabine) overdosage.

Discontinuation of the drug and supportive therapy are of course indicated. Transfusions of platelets should be given if there is any sign of hemorrhage. Patients should be carefully observed for intercurrent infection and if such appears they should be rapidly and rigorously treated with appropriate antibiotic therapy.

Chronic overdosage may cause serious bone marrow suppression. Daily hematological evaluation should be performed to prevent overdosage. Nausea and vomiting, although a general side effect of the drug, may be an additional warning of overdosage. Severe hemorrhage into the gastrointestinal tract may indicate overdosage as may severe generalized infections.

Doses exceeding recommended dosage schedules have been used clinically and have been tolerated. The major toxicity with the use of 3 g/m^2 intravenous infusion over 1 hour every 12 hours for 12 doses and 3 g/m^2 continuous infusion for 4 days, other than reversible bone marrow suppression has been reversible corneal, cerebral and cerebellar dysfunction. Doses of 4.5 g/m^2 intravenous infusion over 1 hour every 12 hours for 12 doses has caused an unacceptable increase in irreversible CNS toxicity and death.

ACTION AND CLINICAL PHARMACOLOGY

Pharmacodynamics

Cytarabine is capable of obliterating immune responses in man during administration. Suppression of antibody responses to E-coli-VI antigen and tetanus toxoid have has been demonstrated. This suppression was obtained 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 has no effect on already established delayed hypersensitivity reactions.

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.

Pharmacokinetics

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

After subcutaneous or intramuscular administration of Cytosar, peak plasma levels of radioactivity are achieved about 20 to 60 minutes after injection and are considerably lower than those after intravenous administration.

Distribution
Cerebrospinal fluid levels of cytarabine are low in comparison to plasma levels after single intravenous injection. However, in one patient in whom cerebrospinal levels were examined after 2 hours of constant intravenous infusion, levels approached 40% 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.

Metabolism
Cytosar (cytarabine) is metabolized by deoxycytidine kinase and other nucleotide kinases to the nucleotide triphosphate, an effective inhibitor of DNA polymerase; it is inactivated by 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.

Excretion
Following rapid intravenous injection of Cytosar, 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, over 80% of plasma radioactivity can be accounted for by the inactive metabolite 1-β-D-arabinofuranosyluracil (ara-U). Within 24 hours about 80% of the administered radioactivity can be recovered in the urine, approximately 90% of which is excreted as ara-U.

Special Populations and Conditions

Hepatic Insufficiency: Use cytarabine with caution or possibly at reduced doses in patients whose liver function is poor (see WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic and DOSAGE AND ADMINISTRATION).

Renal Insufficiency: Use cytarabine with caution or possibly at reduced doses in patients whose kidney function is poor (see WARNINGS AND PRECAUTIONS, Renal and DOSAGE AND ADMINISTRATION).

STORAGE AND STABILITY

Storage

Do not store above 25°C. The expiry date (month/year) is mentioned on the package after “EXP.:” (EXP. = expiry date).

It is shown that chemical and physical in-use stability has been demonstrated 24 hours at 30°C ± 2°C/75% ± 5% RH and for 48 hours at 5°C ± 3°C on reconstituted solution. From a microbiological point of view, unless the method of opening/ reconstitution/ dilution precludes the risk of microbiological contamination, the product should be used immediately.

Chemical Stability and Compatibility

Chemical and physical stability studies of Cytosar have demonstrated that cytarabine is stable for seven days at room temperature when admixed at 0.5 mg/mL in glass i.v. bottles and plastic i.v. bags with: water for injection; 5% Dextrose injection; and 0.9% Sodium Chloride injection solutions. Also when similarly admixed at 8-32 mg/mL in glass i.v. bottles and plastic i.v. bags, cytarabine is stable for seven days at room temperature, -20°C, and 4°C in 5% Dextrose Injection; 5% Dextrose in 0.2% Sodium Chloride Injection; and, in 0.9% Sodium Chloride Injection Solutions.

Cytarabine is stable at room temperature at a concentration of 2 mg/mL in the presence of KCl equivalent to 50 meq/500 mL in Dextrose 5% in water and 0.9% Sodium Chloride for up to eight days.

Cytarabine is also stable at room temperature and at refrigerated temperature (8°C) at a concentration of 0.2-1.0 mg/mL in the presence of sodium bicarbonate equivalent to 50 meq/L in dextrose 5% in water or dextrose 5% in 0.2% sodium chloride for seven days in Travenol glass bottles or Viaflex bags.

Drug Compatibilities

Cytosar 0.8 mg/mL and sodium cephalothin 1.0 mg/mL are chemically stable for 8 hours in dextrose 5% in water.

Cytosar 0.4 mg/mL and prednisolone sodium phosphate 0.2 mg/mL are compatible in dextrose 5% in water for 8 hours.

Cytosar 16 mcg/mL and vincristine sulfate 4 mcg/mL are compatible in dextrose 5% in water for 8 hours.

Drug Incompatibilities

Cytosar has been known to be physically incompatible with heparin, insulin, 5-fluorouracil, penicillin G, and methylprednisolone sodium succinate.

AS WITH ALL INTRAVENOUS ADMIXTURES, DILUTION SHOULD BE MADE JUST PRIOR TO ADMINISTRATION AND THE RESULTING UNPRESERVED SOLUTION USED WITHIN 24 HOURS.

SPECIAL HANDLING INSTRUCTIONS

Caution

The following precautionary measures are recommended in proceeding with the preparation and handling of cytotoxic agents such as Cytosar (cytarabine).

1. The procedure should be carried out in a vertical laminar flow hood (Biological Safety Cabinet - Class II).
2. Personnel should wear: PVC gloves, safety glasses, disposable gowns and masks.
3. All needles, syringes, vials, and other materials which have come in contact with Cytosar should be segregated and destroyed by incineration (sealed containers may explode). If incineration is not available, neutralization should be carried out using 5% sodium hypochlorite, or 5% sodium thiosulfate.
4. Personnel regularly involved in the preparation and handling of Cytosar should have bi-annual haematologic examinations.

DETAILED 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 G_1 phase to 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 has 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.

Animal Studies

In experimental studies with mouse tumors, cytarabine was most effective in those tumors with a high growth fraction. The effect was dependent on the treatment schedule; optimal effects were achieved when the schedule (multiple closely spaced doses or constant infusion) ensured contact of the drug with the tumor cells when the maximum number of cells was in the susceptible S-phase. The best results were obtained when courses of therapy were separated by intervals sufficient to permit adequate host recovery.

TOXICOLOGY

Animal Studies

Toxicity of cytarabine in experimental animals, as well as activity, is markedly influenced by the schedule of administration. For example, in mice, the LD_{10} for single intraperitoneal administration is greater than 6000 mg/m^2. However, when administered in 8 doses, each separated by 3 hours, the LD_{10} is less than 750 mg/m^2 total dose. Similarly, although a total dose of 1920 mg/m^2 administered as 12 injections at 6-hour intervals was lethal to beagle dogs (severe bone marrow hypoplasia with evidence of liver and kidney damage), dogs receiving the same total dose administered as 8 injections (again at 6-hour intervals) over a 48-hour period survived with minimal signs of toxicity.

The most consistent observation in surviving dogs was elevated transaminase levels. In all experimental species the primary limiting toxic effect is marrow suppression with leukopenia. In addition, cytarabine causes abnormal cerebellar development in the neonatal hamster and is teratogenic to the rat fetus.

The major dose-limiting toxicity of cytarabine observed in all tested species is myelosuppression, manifested by megaloblastosis, reticulocytopenia, leukopenia, and thrombocytopenia. Other target organs include liver, kidney, and brain. Extensive chromosomal damage, including chromatoid breaks have been produced by cytarabine and malignant transformation of rodent cells in culture has been reported. Cytarabine is embryotoxic and teratogenic and produced peri- and postnatal toxicity in various species. No formal fertility studies have been reported however sperm head abnormalities were observed following cytarabine treatment in mice.

APPENDIX A

LSA_2-L_2 Protocol

Woolner N, Burchenal JH, Lieberman PH, *et al*: Non-Hodgkin's Lymphoma in Children - A Comparative Study of Two Modalities of Therapy. *Cancer* 1976;37:123-134.

Induction Phase

Day 1.	Cyclophosphamide 1,200 mg/m^2 single push injection.
Day 3 to 31.	Prednisone 60 mg/m^2 po divided into three daily doses.
Day 3, 10, 17, 24.	Vincristine 1.5 to 2.25 mg/m^2 intravenously.
Day 5, 27, 30.	Spinal tap and intrathecal injection of Methotrexate 6.25 mg/m^2.
Day 12, 13.	Daunomycin 60 mg/m^2 intravenously.

At the end of induction (last dose of intrathecal methotrexate) patient rests for 3-5 days before consolidation.

Consolidation Phase

Day 34 or 36, daily intravenous injections of cytosine arabinoside (Ara-C) 150 mg/m^2 for a total of 15 injections are given. (Injections are given from Monday through Friday.) Thioguanine 75 mg/m^2 is given orally, 8-12 hours after the injection of Ara-C. If the white blood count is 1500 or more and the platelet count 150,000 or more on the 5th day of Ara-C, the patient continues to receive the same dosage of thioguanine over the weekend. However, both are discontinued temporarily when there is evidence of marrow depression; this usually occurs after the initial seventh to tenth doses of the combination and ordinarily recovers within 7-10 days. Hence, the patients may receive more than 15 doses of thioguanine orally, but receive only 15 doses of i.v. cytosine arabinoside (Ara-C). This first phase of the consolidation takes an average of 30-35 days. The second phase of the consolidation should be started immediately after completion of the 15 doses of Ara-C; it entails daily i.v. administration of L-asparaginase, 60000 U/m^2 for a total of 12 injections, excluding weekends.

Two days after the last injection of the L-asparaginase, two more intrathecal (i.t.) injections of methotrexate are given 2 days apart. Three days after the last i.t. methotrexate, BCNU [1, 3-Bis (2 chloroethyl 1-1-nitrosourea)] 60 mg/m^2 is given i.v., which completes the consolidation. The average duration of the induction and consolidation is 85-100 days.

Maintenance Phase

The maintenance period consists of five cycles of 5 days each and is started 3-4 days after completion of consolidation.

Cycle I: Oral thioguanine 300 mg/m^2 for 4 consecutive days: i.v. cyclophosphamide 600 mg/m^2 on the 5^{th} day.
Rest 7-10 days.

Cycle II: Oral hydroxyurea 2,400 mg/m^2 for 4 consecutive days: i.v. daunomycin 45 mg/m^2 on the 5^{th} day.
Rest 7-10 days.

Cycle III: Oral methotrexate 10 mg/m^2 for 4 consecutive days: i.v. BCNU 60 mg/m^2 on the 5^{th} day.
Rest 7-10 days.

Cycle IV: I.V. Ara-C 150 mg/m^2 for 4 consecutive days: i.v. vincristine 1.5 mg/m^2 on Day 5.
Rest 7-10 days.

Cycle V: Two doses of i.t. methotrexate 6.25 mg/m^2 2-3 days apart.
Rest 7-10 days and restart with Cycle I.

March 2021
Hong Kong