Drug Monograph

A - Drug Name

cytarabine

SYNONYM(S): Ara-C; Arabinosylcytosine; Cytosine Arabinoside

COMMON TRADE NAME(S): Cytosar® (multiple brands available)

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B - Mechanism of Action and Pharmacokinetics

Cytarabine is metabolized intracellularly into its active triphosphate form (cytosine arabinoside triphosphate), which competes with deoxycytidine triphosphate, the physiologic substrate of DNA polymerase. This metabolite damages DNA by multiple mechanisms including the inhibition of DNA polymerase or incorporation into DNA. It is inactivated by pyrimidine nucleoside deaminase. Cytotoxicity is highly specific for the S phase of the cell cycle.

Absorption	Bioavailability	oral: Poorly absorbed from gastrointestinal tract; <20% bioavailability
Distribution	Rapidly and widely distributed into tissues, including liver, plasma, and peripheral granulocytes. Also crosses the placenta.	
	Cross blood brain barrier?	CSF : plasma ratio - 40-60% (infusion or SC), less with rapid IV infusion
	PPB	13 %
Metabolism	Rapid and extensive metabolism by cytidine deaminases mainly in liver and kidneys.	
	Active metabolites	Cytarabine triphosphate

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	Inactive metabolites	Uracil arabinoside
Elimination	Cytarabine and its inactive metabolite are excreted in urine. Clearance of intrathecal dose is by CSF bulk flow and diffusion to plasma; CSF levels of deaminase are low.	
	Urine	70-80% within 24 hours (90% as inactive metabolite, 10% as intact drug)
	Half-life	$t_{½\ \alpha}$ = 10 minutes; $t_{½\ ß}$ = 1-3 hours

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C - Indications and Status

Health Canada Approvals:

- Induction and maintenance of acute leukemia in adults and children
- Acute myelocytic leukemia
- Chronic myelogenous leukemia (blast phase)
- Acute lymphocytic leukemia
- Erythroleukemia
- Non-Hodgkin’s lymphoma (pediatric)
- Meningeal leukemia (intrathecal)
- Poor-risk, refractory and relapsed acute leukemia

Other Uses:

- Hodgkin's lymphoma
- Burkitt's lymphoma
- Non-Hodgkin's lymphomas (adults)

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D - Adverse Effects

Emetogenic Potential: Low (≤ 200 mg/m2, low dose cytarabine)
Moderate (> 200 mg/m2, high dose cytarabine)

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Extravasation Potential: None

The side effects reported below were from conventional dose therapy, unless specified as high dose. Frequency is unknown, unless specified.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Cardiomyopathy (high doses especially with cyclophosphamide)	E
	Pericarditis	E
Dermatological	Alopecia (>10%) (more common with high doses)	E
	Hand-foot syndrome (may be severe)	E
	Rash (>10%) (may be severe with desquamation)	E
	Skin hyperpigmentation (freckling)	E
Gastrointestinal	Anorexia	E
	Colitis (1-10%; necrotizing- with high dose)	E
	Diarrhea (>10%)	E
	GI perforation (or ulcer, high dose)	E
	Mucositis (>10%)	E
	Nausea, vomiting (>10%)	I E
	Typhlitis (<10%)	E
General	Flu-like symptoms (>10%)	I E
Hematological	Myelosuppression ± infection, bleeding (>10%)	E
Hepatobiliary	↑ LFTs (>10%) (may be severe)	E
	Pancreatitis	E
Hypersensitivity	Drug reaction (type 1 - anaphylactoid, rare)	I
Injection site	Injection site reaction (pain, inflammation - rare; thrombophlebitis)	I E
Metabolic / Endocrine	Tumor lysis syndrome (rare)	E
Nervous System	Dizziness	E
	Headache	E
	Leukoencephalopathy (paraplegia, arachnoiditis; with high dose or IT use)	E
	Peripheral neuropathy (or neuritis; high dose)	E

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	Personality change (high dose)	I E
	Seizure (high dose)	I E
	Somnolence (>10%) (depressed level of consciousness with high dose)	E
Ophthalmic	Conjunctivitis (with high doses)	E
	Other (>10%) (corneal toxicity - with high doses)	E
Renal	Renal failure	E
Respiratory	Adult respiratory distress syndrome (ARDS) (>10%) (high doses)	E
	Dyspnea	E
	Pneumonitis	E

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.
Dose-limiting side effects are underlined.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common side effects for cytarabine include ↑ lfts, flu-like symptoms, mucositis, myelosuppression ± infection, bleeding, nausea, vomiting and rash.

Myelosuppression is the most common toxicity seen with cytabarine treatment. **GI effects** (nausea, vomiting, diarrhea, mucositis, abdominal pain and transaminitis) are commonly described. Toxicity is schedule dependent – higher doses can usually be tolerated when cytarabine is administered as a rapid IV infusion, although GI toxicity is more problematic.

Hyperuricemia and **tumour lysis** may occur if there is a rapid response and a high tumour burden. Patients at risk of tumour lysis syndrome should have appropriate prophylaxis and be monitored closely.

Cytarabine syndrome may develop with fever, myalgia, bone pain and rash, usually occurring 6-12 hours following drug administration. Symptoms usually disappear when drug is discontinued and may be treated or prevented with corticosteroids.

Elevations in liver function tests occur with both standard and high dose regimens.

Adverse effects from **high-dose cytarabine** (2-3 g/m^2) include severe and occasionally fatal CNS, cardiovascular, gastrointestinal or pulmonary toxicity, as well as corneal toxicity or conjunctivitis (may be hemorrhagic). Ocular toxicity is minimized by prophylactic use of ophthalmic corticosteroids. Use prednisolone 1% or dexamethasone 0.1%, 2 drops in each eye q4h beginning before the first dose of cytarabine and continuing until 48 hours after the last one.

Neurotoxicity is more common in older patients and in patients with renal or hepatic impairment.

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Peripheral neuropathy may occur rarely with high doses and may be irreversible. Cerebellar and cerebral toxicity, especially with high doses in patients with renal or hepatic impairment may occur. Seizures, if they occur, are usually self-limited and do not recur once therapy is stopped. In most patients, neurologic dysfunction resolves in 5-10 days, but in some patients toxicity may be irreversible or fatal. Dose modification is required.

Fatal **delayed progressive ascending paralysis** has been reported in children with AML following conventional-dose cytarabine (IT/IV) in combination with other medications).

Adverse effects associated with **intrathecal cytarabine** are generally mild and include nausea and vomiting, headache and fever. Paraplegia, neuropathy, leukoencephalopathy and blindness were reported rarely. The risk is increased with intrathecal administration within a few days of intravenous cytarabine.

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E - Dosing

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response and concomitant therapy. Guidelines for dosing also include consideration of white blood cell count. Dosage may be reduced and/or delayed in patients with bone marrow depression due to cytotoxic/radiation therapy. Benzyl alcohol diluent should NOT be used for high dose or intrathecal administration.

Adults:

Induction:

- q2w: 200 mg/m^2/day x 5 days - continuous infusion
- q2-4w: 100 mg/m^2/day x 7-10 days - continuous infusion

Maintenance:

- May be given: refer to specific treatment protocols for doses and schedules

High-dose:

- q2-3w: 2-3 g/m^2 over 1-3 hours q12h x 4-12 doses

Intrathecal:

- 30mg/m^2 (5-75mg/m^2) every 4 days until CSF clear
- May be used in combination with methotrexate and hydrocortisone as triple therapy, or

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alternating with methotrexate. Refer to specific treatment protocol for doses and schedules.

Dosage with Toxicity:

Dosage in myelosuppression: Modify according to protocol by which patient is being treated; must be under the care of a specialized hemato-oncologist.

Dosage with Hepatic Impairment:

Reduce dose with impaired liver function. No details found; use with extreme caution.

Dosage with Renal Impairment:

No adjustment required for standard doses. For high-dose therapy, since renal impairment (< 60 mL/min) is a risk factor for neurotoxicity, consider:

- dose reduction (3 g/m^2→ 2 g/m^2→ 1 g/m^2→ 0.1 g/m^2/day CIV)
- schedule modification (i.e. from q12h to q24h)

Children:

The safety of cytarabine in infants (< 1 year) has not been established.

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F - Administration Guidelines

- May be given as an IV infusion, IM, SC or IT injection.
- DO NOT use benzyl alcohol diluent with high dose cytarabine, IT use or in infants.
- May be mixed in 50-100mL minibag (Normal Saline – preferred, or 5% Dextrose); Infuse over approximately 15 – 60 minutes.

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- Larger doses may be mixed in 250mL bag (Normal Saline – preferred, or 5% dextrose); Infuse IV over 1-3 hours.
- May be given by direct IV push, followed by a Normal Saline flush, if no IV line has been set up.
- Continuous infusion using CADD infusion pump, or similar device; Infuse through central venous access device.
- Incompatible with heparin, insulin, 5-fluorouracil, penicillin G and methylprednisolone sodium succinate.
- May be given as an intrathecal injection; mix in preservative-free normal saline (DO NOT USE BENZYL ALCOHOL DILUENT) using strict aseptic technique and use immediately.

Storage/stability:

Diluted, unpreserved cytarabine solutions should be used within 24 hours at room temperature. Refer to the cytarabine product monograph for longer-term stability information.

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G - Special Precautions

Contraindications:

- patients who have a hypersensitivity to this drug or any of its components
- formulation/diluent containing benzyl alcohol should not be used for intrathecal use, high dose regimens or in neonates

Other Warnings/Precautions:

- extreme caution should be used with high dose therapy especially in older patients, patients with hepatic or renal impairment, pre-existing CNS, cardiovascular or pulmonary disease.
- avoid live vaccines

Other Drug Properties:

- Carcinogenicity: Probable

Pregnancy and Lactation:

- Embryotoxicity: Probable
- Teratogenicity: Probable
- Mutagenicity: Probable
  Cytarabine is contraindicated in pregnancy and may be present in semen. Adequate contraception should be used by both sexes during treatment, and for at least 6 months after the last dose.
- Excretion into breast milk: Probable
  Breastfeeding is not recommended.

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- Fertility effects: Probable
  No formal fertility studies have been conducted in humans.

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H - Interactions

AGENT	EFFECT	MECHANISM	MANAGEMENT
Digoxin	↓ efficacy of digoxin	↓ absorption due to damage to intestinal mucosa by cytarabine	Monitor levels
Aminoglycosides	↓ aminoglycoside effect in vitro	Unknown	monitor levels
flucytosine	↓ flucytosine effect	possible competitive inhibition of flucytosine uptake by fungi	increase dose of flucytosine
Cyclophosphamide	Increased cardiomyopathy and sudden death with high dose cytarabine used for BMT conditioning regimens	Additive	Avoid with high dose cytarabine
Methotrexate IT	Increased risk of severe neurological effects when given with cytarabine IV	Additive	Avoid concomittant administration

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Note: high dose regimens require intensive monitoring

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
CBC	Baseline and before each dose; more frequent as clinically indicated
Renal function tests (including uric acid)	Baseline and before each dose
Liver function tests	Baseline and before each dose

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Clinical assessment of GI, CNS, pulmonary, skin, ocular toxicity, infection and bleeding	At each visit

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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K - References

Cancer Drug Manual (the Manual), revised December 2013, British Columbia Cancer Agency (BCCA).

McEvoy GK, editor. AHFS Drug Information 2009. Bethesda: American Society of Health-System Pharmacists, p. 1014-20.

NCI Drug Dictionary. Accessed May 25, 2011.

Product Monograph: Cytosar® (cytarabine). Pfizer Canada, August 2015.

Smith GA, Damon LE, Rugo HS, et al: High-dose cytarabine dose modification reduces the incidence of neurotoxicity in patients with renal insufficiency. J Clin Oncol 1997; 15(2): 833-839.

November 2017 republished under correct website filters. No changes.

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