

DRUG NAME: Cytarabine**SYNONYM(S):** 1-B-arabinofuranosylcytosine,¹ arabinosylcytosine,¹ ara-C,¹ cytosine arabinoside¹**COMMON TRADE NAME(S):** CYTOSAR®**CLASSIFICATION:** antimetabolite¹*Special pediatric considerations are noted when applicable, otherwise adult provisions apply.***MECHANISM OF ACTION:**

Cytarabine, a synthetic pyrimidine nucleoside, is converted intracellularly, primarily by deoxycytidine kinase, to active cytarabine triphosphate.^{1,2} Activity occurs primarily as the result of inhibition of DNA polymerase via competition with deoxycytidine triphosphate, resulting in the inhibition of DNA synthesis.² Incorporation of cytarabine into DNA and RNA may contribute to cytotoxic effects.² Cytarabine also has antiviral and immunosuppressive properties.²⁻⁴ Cytarabine is cell cycle phase-specific for the S-phase; cytarabine may also block progression from the G1-phase to the S-phase.² Both concentration and duration of exposure are critical for cytotoxicity.⁵

PHARMACOKINETICS:

Oral Absorption	<20%; ineffective when administered orally ¹	
Distribution	wide and rapid distribution into tissues and fluids ^{1,2} ; crosses the placenta SC or IM: peak levels in 20-60 min, considerably lower peak levels than those obtained after IV ¹ IT: most of dose diffuses into systemic circulation, but is rapidly metabolized	
	cross blood brain barrier?	limited; CIVI or SC: CSF concentration \leq 60% that of plasma, less after rapid IV ⁶
	volume of distribution ⁷	2.6 L/kg
	plasma protein binding	13%
Metabolism	rapid and extensive; primarily hepatic; also metabolized in the kidneys, GI mucosa, granulocytes, and other tissues by cytidine deaminase ¹ ; minimal metabolism in CSF ^{3,6}	
	active metabolite	cytarabine triphosphate
	inactive metabolite	uracil arabinoside
Excretion	urine	70-80%; 90% as uracil arabinoside, 10% unchanged
	feces	no information found
	terminal half life	1-3 h; variable ⁴ IT: 2-4 h in CSF ⁵
	clearance	IT: 0.42 mL/min ⁸

Adapted from standard reference² unless specified otherwise.**USES:****Primary uses:**

- *Leukemia, acute lymphocytic
- *Leukemia, acute myeloid
- *Leukemia, chronic myelogenous
- *Leukemia, meningeal and other meningeal neoplasms (intrathecal)
- *Lymphoma, non-Hodgkin's; childhood

*Health Canada approved indication

Other uses:

- Lymphoma, Hodgkin's^{2-4,6}
- Lymphoma, non-Hodgkin's; adult^{1,3,4,6}
- Myelodysplastic syndrome⁴

SPECIAL PRECAUTIONS:**Caution:**

- Use cytarabine with caution in patients with pre-existing drug-induced bone marrow suppression or impaired hepatic function.²
- Because of potential toxicity, do not use products containing benzyl alcohol or products reconstituted with preserved diluent intrathecally, for neonates, or for high-dose cytarabine regimens.²
- High-dose therapy (2,000-3,000 mg/m²) may cause severe and sometimes fatal CNS, GI, and pulmonary toxicities.²

Carcinogenicity: Cytarabine is potentially carcinogenic.¹

Mutagenicity: Mutagenic in Ames test and mammalian *in vitro* mutation test. Cytarabine is clastogenic in mammalian *in vitro* and *in vivo* chromosome tests.⁹

Fertility: Both reversible and irreversible germ cell toxicity has been reported with cytarabine.^{4,10} The total dose below which there is no risk to fertility has not been established. Prediction of the degree of testicular or ovarian function impairment is complicated by several variables, including the route of administration, dose and length of therapy, frequency of treatment, and the use of combination therapy.^{4,10}

Pregnancy: FDA Pregnancy Category D.⁴ There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).

Breastfeeding is not recommended due to the potential secretion into breast milk.²

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.¹¹ When placebo-controlled trials are available, adverse events are included if the incidence is \geq 5% higher in the treatment group.

High-dose is defined as 2,000-3,000 mg/m².

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in bold, italics	
allergy/immunology	anaphylaxis with acute cardiopulmonary arrest (<1%)
	cutaneous small vessel necrotizing vasculitis ^{3,6} ; with high-dose ³
blood/bone marrow/ febrile neutropenia	<i>anemia; megaloblastic anemia (<2%)⁴</i>
	<i>leukopenia (>15%),⁴ neutropenia; onset within 24 hours, 1st nadir at 7-9 days with a brief recovery day 12, 2nd nadir greater than the first, at 15-24 days, recovery in the following 10 days</i>
	<i>thrombocytopenia (>15%)⁴; onset 5 days, nadir 12-15 days, recovery in the following 10 days</i>
cardiovascular (general)	cardiomyopathy, cardiomegaly ¹²
	pericarditis with tamponade (<0.1%) ⁶ ; increased incidence with high-dose ⁶ ; onset typically days after initiating treatment ⁶
constitutional symptoms	fever (>80%) ¹² ; unrelated to infection
	weight gain; transient, secondary to severe intestinal toxicity

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in bold, italics	
dermatology/skin	<i>extravasation hazard: none</i> ¹³
	alopecia ($\leq 10\%$) ⁴ ; more frequent and complete with high-dose
	freckling ($\leq 10\%$) ⁴
	injection site reactions; pain and inflammation ($\leq 2\%$), ^{4,14} thrombophlebitis, or cellulitis
	pruritis ⁴ ($\leq 10\%$) ⁴
	<i>rash (severe <1%); particularly affecting palms and soles of the feet,</i> ^{15,16} <i>increased incidence with high-dose</i>
	skin ulcerations
gastrointestinal	<i>emetogenic potential</i> ¹⁷ : dose-related; high-moderate for > 1,000 mg/m ² , low for 100-200 mg/m ²
	anorexia ($\geq 15\%$) ⁴
	<i>bowel necrosis, necrotizing colitis including oral and anal ulcerations, and pneumatosis cystoides intestinalis leading to peritonitis; with high-dose</i>
	diarrhea ($\leq 10\%$) ⁴
	esophagitis ($\leq 2\%$) ⁴
	ileus
	mucositis ($\geq 15\%$) ⁴ ; severe with high-dose
	<i>nausea and vomiting ($\leq 2\%$)⁴; more frequent and severe with rapid IV administration of high-dose</i>
	protein-losing enteropathy
hemorrhage	hemorrhagic conjunctivitis ⁴ ; reversible ⁴
	gastrointestinal hemorrhage ($\leq 2\%$) ⁴
hepatobiliary/pancreas	hepatic dysfunction ($\leq 2\%$) ⁴ ; increased incidence with high-dose
	pancreatitis
infection	<i>infections, not otherwise specified; complicated by peritonitis, or liver abscesses; with high-dose</i> <i>intestinal infection</i>
	<i>sepsis; with high-dose</i>
metabolic/laboratory	elevated amylase ¹²
	elevated lipase ¹²
	elevated transaminases and alkaline phosphatase
	hyperbilirubinemia
	hyperuricemia ($\leq 10\%$) ⁴
	hypocalcemia
	hypokalemia
musculoskeletal	rhabdomyolysis; with high-dose ⁶
neurology	dizziness ($\leq 10\%$) ⁴
	<i>neurotoxicity (5-50%)⁴; increased incidence with high-dose, see paragraph regarding high-dose therapy following Side Effects table</i>

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in bold, italics	
	seizures (<1%); with IT
	somnolence; increased incidence with high-dose
ocular/visual	ocular toxicity , see paragraph regarding high-dose therapy following Side Effects table
pain	pain including: abdominal pain, bone pain, ¹² chest pain, myalgia, ¹² and sore throat
pulmonary	pulmonary toxicity ($\leq 2\%$) ⁴ ; with relatively high-dose (e.g., $\geq 1,000$ mg/m ²), see paragraph regarding high-dose therapy following Side Effects table
renal/genitourinary	renal dysfunction
	urinary retention ($\leq 2\%$) ⁴
sexual/reproductive function	germ cell toxicity; reversible and irreversible ⁴
syndromes	cytarabine syndrome ($\leq 2\%$) ⁴ ; see paragraph following Side Effects table
	syndrome of sudden respiratory distress ($\leq 16\%$) ^{4,18} ; see paragraph regarding high-dose therapy following Side Effects table
	tumour lysis syndrome; with high-dose ¹²
vascular	veno-occlusive disease ¹²

Adapted from standard reference² unless specified otherwise.

Cytarabine syndrome, a flu-like syndrome, characterized by fever, myalgia, bone pain, maculopapular rash, conjunctivitis, malaise, and occasionally chest pain, may begin 6-12 h after IV cytarabine.² This syndrome occurs more commonly after large doses; however, it can occur with small doses,⁶ and has occurred after initial or subsequent courses of therapy.^{19,20} A hypersensitivity mechanism may be responsible.^{6,19} Symptoms usually resolve within 24 hours when cytarabine is discontinued; corticosteroids may be used for treatment and prophylaxis.^{1,2,19} Cytarabine therapy may be continued with corticosteroid prophylaxis.^{1,2,19}

Administration: Higher total doses are generally better tolerated when given by rapid IV injection compared to continuous IV infusion;¹⁻³ however, GI effects may be more pronounced with rapid IV injection.^{4,12} The rate of administration does not affect the incidence of hematological toxicities.^{1,3} This difference in tolerability may be due to the rapid clearance of cytarabine.²

High-dose therapy (2,000-3,000 mg/m²) has been associated with severe and potentially fatal toxicities which differ from those seen with usual low doses.

- Ocular toxicities may include vision loss, reversible corneal toxicity (keratitis), and hemorrhagic conjunctivitis ($\leq 80\%$).^{2,3,6} Ocular toxicities have been reported 1-2 weeks after initiating therapy.⁶ Symptoms may include tearing, eye pain, foreign body sensation, photophobia, and blurred vision.⁶ Conjunctivitis may occur with rash. Toxicity can be minimized by prophylactic use of ophthalmic corticosteroids.² Use prednisolone 0.12% - 1% or dexamethasone 0.1%,^{12,21} 2 drops in each eye every 4 hours, beginning before the first dose of cytarabine and continuing until 48 hours after the last one.²¹ NS may also help relieve symptoms.¹²
- Neurotoxicity (8-10%) typically occurs 3-8 days after initiating therapy.^{2,4,12,22} Cerebellar dysfunction is characterized by difficulty with speech, trouble standing or walking, and tremors. Cerebral dysfunction may be seen concomitantly and is characterized by somnolence, confusion, personality changes, cognitive dysfunction, memory loss, psychosis, or seizures. Seizures are usually self-limited. In most patients, neurologic dysfunction resolves in 5-10 days. There is a high incidence (~60%) of recurrent cerebellar toxicity in patients who have already experienced toxicity. It is not conclusively known if cytarabine therapy should be discontinued if neurological toxicity develops.²³

Risk factors for developing cerebellar toxicity include: age over 50 years,^{3,6} impaired renal function^{3,6} (CrCl <60 mL/min),²² and total dose received.^{6,22} Prior CNS disease may also be risk factors.⁶ Methods used to decrease the risk of neurotoxicity in these patients include: decreasing the dose, utilizing a once-daily rather than twice-daily schedule, shortening the course of treatment, and modifying the dose based on the CrCl.^{6,23,24}

Peripheral motor and sensory neuropathies involving both upper and lower extremities have occurred. Neuropathies may manifest as muscle weakness, gait disturbances, paresthesias, myalgia, hypoalgesia, and hypoesthesia.¹ Dose adjustments may be required to avoid irreversible complications.¹

- Gastrointestinal toxicities may include GI ulceration, bowel necrosis, and necrotizing colitis including pneumatosis cystoides intestinalis leading to peritonitis.^{1,2} GI effects may be more pronounced with rapid IV injection compared to continuous IV infusion.¹²
- Pulmonary toxicities may include interstitial pneumonitis, noncardiogenic pulmonary edema, and a potentially fatal syndrome of sudden respiratory distress (SRD) that includes cough, dyspnea, fever, tachypnea, hypoxemia, pneumonia, and interstitial and alveolar infiltrates progressing to pulmonary edema and cardiomyopathy.^{2,12,18} Pulmonary edema typically occurs 1-2 weeks after therapy, often after the first course.¹⁸ Pulmonary toxicities may correlate with the gastrointestinal lesions seen with cytarabine.⁶ Capillary leak syndrome may also be a factor in the development of SRD.⁶ Continuous infusions may be more likely than intermittent infusions to cause SRD.⁶ Treatment measures include supportive care, high-dose corticosteroids,⁶ and discontinuing cytarabine.
- Pancreatitis and hepatic injury.²
- Palmar-plantar erythrodysesthesia,^{2,12,15,16} leading to desquamation,² may occur with intermediate or high-dose therapy.³ Prophylactic topical steroids and/or skin moisturizers may be used.¹²
- Fatal cardiomyopathy.¹

Tumour lysis syndrome may result from cell lysis by cytotoxic chemotherapy and may lead to electrolyte disturbances or acute renal failure.²⁵ It is most likely with highly proliferative tumours of massive burden, such as leukemias, high-grade lymphomas, and myeloproliferative diseases. The risk may be increased in patients with preexisting renal dysfunction, especially ureteral obstruction. Suggested prophylactic treatment for high-risk patients²⁶:

- aggressive hydration: 3 L/m²/24 hr with target urine output >100 ml/h
- if possible, discontinue drugs that cause hyperuricemia (e.g., thiazide diuretics) or acidic urine (e.g., salicylates)
- monitor electrolytes, calcium, phosphate, renal function, LDH, and uric acid q6h x 24-48 hours
- replace electrolytes as required
- allopurinol 600 mg po initially, then 300 mg po q6h x6 doses, then 300 mg po daily x 5-7 days

Urine should be alkalinized only if the uric acid level is elevated, using sodium bicarbonate IV or PO titrated to maintain urine pH>7. Rasburicase (FASTURTEC®) is a novel uricolytic agent that catalyzes the oxidation of uric acid to a water-soluble metabolite, removing the need for alkalinization of the urine.²⁷ It may be used for treatment or prophylaxis of hyperuricemia; however, its place in therapy has not yet been established. Aluminium hydroxide (e.g., AMPHOGEL®) may be added orally if phosphate becomes elevated. If aluminium hydroxide has been added, discontinue sodium bicarbonate.²⁸

Intrathecal administration: Side effects from intrathecal cytarabine administration are generally mild and self-limiting. Rarely, severe systemic toxicities have been reported.² The most frequent of these are nausea, vomiting, and fever.² Transient headaches may occur in up to 10% of patients.⁴ Intrathecal use of cytarabine has rarely been associated with neurotoxicities including meningism, paresthesia, paraplegia, spastic paraparesis, and seizures.¹ Blindness and necrotizing leukoencephalopathy have also been reported in patients receiving cytarabine in combination with other chemotherapeutic agents and/or radiation.^{1,14} Cytarabine neurotoxicity has been linked to diluents containing preservatives²; use preservative-free diluents when preparing cytarabine for intrathecal use.² Administering cytarabine IT and IV within a few days of each other may increase the risk of neurotoxicity.¹

Sustained-release formulation for intrathecal administration: A suspension of cytarabine encapsulated within a multivesicular lipid-based particle (DEPOCYT® 10 mg/mL), is available for intrathecal use. This sustained-release formulation of cytarabine has a half life in the CSF of 100-263 hours.²⁹ Patients receiving liposomal cytarabine should receive dexamethasone 4 mg bid IV or PO for 5 days starting on day 1 to decrease the incidence of chemical arachnoiditis. Chemical arachnoiditis typically manifests as back pain, neck stiffness or pain, nausea and vomiting, headache, and fever.^{3,9,29} Adverse effects associated with liposomal cytarabine typically occur within 5 days of administration.⁹ The recommended dosage regimen for liposomal cytarabine is as follows²⁹:

- Induction therapy: 50 mg intrathecally every 14 days for 2 doses (weeks 1 and 3).
- Consolidation therapy: 50 mg intrathecally every 14 days for 3 doses (weeks 5, 7 and 9) followed by 1 additional dose at week 13.
- Maintenance: 50 mg intrathecally every 28 days for 4 doses (weeks 17, 21, 25 and 29).
- If drug-related neurotoxicity develops, reduce the dose to 25 mg. If toxicity persists, discontinue treatment.

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
ciprofloxacin ³⁰	decreased effect of ciprofloxacin	cytarabine-induced changes to intestinal mucosa cause a decrease in absorption of ciprofloxacin	monitor for response to ciprofloxacin, adjust ciprofloxacin dose as needed
digoxin ^{1,2,30}	decreased effect of digoxin tablets	cytarabine-induced changes to intestinal mucosa cause a decrease in absorption of digoxin tablets	consider monitoring digoxin levels, adjust digoxin dose as needed
fludarabine ^{3,31,32}	fludarabine given first appears to increase the therapeutic effects of cytarabine, cytarabine given first appears to inhibit the antineoplastic effect of fludarabine	fivefold increase in intracellular cytarabine concentrations in leukemic cells when fludarabine is given first, likely due to competition for deoxycytidine kinase, needed to convert both drugs to their active triphosphate	clinical importance as yet unknown

Theoretical: decreased *in vitro* effect of gentamycin against *Klebsiella pneumoniae* via antagonism of gentamycin activity by cytarabine. In the treatment of infections caused by *Klebsiella pneumoniae*, monitor for response to gentamycin. If a response is not achieved, consider alternate antibiotic therapy.^{2,30}

SUPPLY AND STORAGE:

Injection:

Pfizer Canada Inc supplies cytarabine as a sterile solution for injection without preservative in 100 mg (5 mL) and 500 mg (25 mL) single use vials at a concentration of 20 mg/mL and in 1000 mg (10 mL) and 2000 mg (20 mL) single use vials at a concentration of 100 mg/mL. Store at room temperature. Protect from light.³³

Hospira Healthcare Corporation supplies cytarabine as a sterile solution without preservative in single use vials of 100 mg (1mL), 500 mg (5mL), 1000 mg (10 mL), and 2000 mg (20 mL) at a concentration of 100 mg/mL. Store at room temperature. Protect from light.³⁴

For basic information on the current brand used at the BC Cancer Agency, see [Chemotherapy Preparation and Stability Chart](#) in Appendix.

SOLUTION PREPARATION AND COMPATIBILITY:

For basic information on the current brand used at the BC Cancer Agency, see [Chemotherapy Preparation and Stability Chart in Appendix](#).

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

BCCA administration guideline noted in **bold, italics**

Subcutaneous	has been used; continuous SC infusions have also been used ^{1,2}
Intramuscular	has been used ¹
Direct intravenous	has been used²
*Intermittent infusion	over ≥ 15 min for doses⁶ $< 1,000$ mg/m² ; over 1-3 h for high-dose²
*Continuous infusion	has been used²
Intraperitoneal	no information found
Intrapleural	no information found
[†] Intrathecal	qs to 6 mL with preservative-free NS³⁵⁻³⁷ alternatively may be diluted in 5-15 mL of solution to achieve a concentration of 5 mg/mL ² children: dilute in 5-15 mL of solution to achieve a concentration of 5 mg/mL ² liposomal cytarabine: over 1-5 min ²⁹
Intra-arterial	no information found
Intravesical	no information found

*High-dose cytarabine requires preservative-free diluent.²

[†]Intrathecal cytarabine requires preservative-free cytarabine and diluent. See [BC Cancer Agency Policy III-50 Administration of Cytotoxic Drugs by the Intrathecal Route via Lumbar Puncture or Ommaya Reservoir](#) in Appendix.

DOSAGE GUIDELINES:

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 absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

Adults:

BCCA usual dose noted in **bold, italics**

<i>Intravenous:</i>	Cycle Length: 2 weeks ^{1,2,6} :	200 mg/m ² IV over 24 hours for 5 consecutive days starting on day 1 (total dose per cycle 1000 mg/m ²)
	2-4 weeks ^{1,2,6} :	100 mg/m ² (range 100-200 mg/m ²) IV over 24 hours (or divided in 2 or 3 doses) for 7 consecutive days (range 5-10 days) starting on day 1 (total dose per cycle 700 mg/m ² [range 500-2,000 mg/m ²])

BCCA usual dose noted in **bold, italics**

	Cycle Length: <i>High-dose therapy</i> ^{2,4,6,12,23} :	3,000 mg/m ² (range 1,000-3,000 mg/m ²) IV every 12 hours for 2-6 consecutive days starting on day 1 (total dose range 4,000-36,000 mg/m ²) note: high-dose therapy should only be used by physicians experienced in managing its side effects
Subcutaneous:	4-6 weeks ^{38,39} :	20 mg SC twice daily for 10 consecutive days (total dose per cycle 400 mg)
	1-4 weeks ² :	1 mg/kg (range 1-1.5 mg/kg) SC for one dose on day 1 (total dose per cycle 1 mg/kg [range 1-1.5 mg/kg])
	4 weeks ⁴⁰ :	20 mg/m ² SC once daily for 10 consecutive days (total dose per cycle 200 mg/m ²)
	n/a ² :	10-20 mg SC daily (or divided) for 21-42 consecutive days (total dose 210-840 mg)
Intrathecal:	1 week ^{35,36} :	50 mg IT for one dose once weekly (range once or twice weekly) (maximum two IT injections per week) (total dose per cycle 50 mg/m² [range 50-100 mg/m²])
	n/a ² :	30 mg/m ² (range 5-75 mg/m ²) IT for one dose every 4 days (range 2-7 days) until CSF findings normalize, typically followed by one additional dose
	n/a ³⁷ :	50 mg IT for one dose on day 1 (total dose per cycle 50 mg/m²)
Concurrent radiation:		irradiation erythema has been reported in patients who have received radiation ¹⁶
Concurrent chemotherapy:		adjustment of concurrent systemic chemotherapy may be required when administering intrathecal cytarabine ²
Dosage in myelosuppression:		modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix 6 "Dosage Modification for Myelosuppression"
Dosage in renal failure:		no adjustment required ^{2,7} ; for high-dose therapy the following dose-modification algorithm may be used to minimize neurotoxicity ¹² ; the risk of neurotoxicity with high-dose cytarabine is directly related to renal function throughout therapy, ⁶ see paragraph following Side Effects table

Creatinine clearance (mL/min)	Dose
>60	100%
46-60	60%
31-45	50%
< 30	discontinue, consider alternate therapy

$$\text{Calculated creatinine clearance} = \frac{N * (140 - \text{Age}) \times \text{weight (kg)}}{\text{Serum Creatinine in } \mu\text{mol/L}}$$

* For males N = 1.23; for females N=1.04

BCCA usual dose noted in ***bold, italics***

Dosage in hepatic failure: Cycle Length:
dose reduction may not be necessary^{1,2}; if adjusted the following guideline has been used¹²:
a 50% initial dose reduction if bilirubin \geq 34 $\mu\text{mol/L}$ and increase as tolerated

Dosage in dialysis:

- hemodialysis: supplemental dose is not necessary¹²
- continuous ambulatory peritoneal dialysis (CAPD): supplemental dose is not necessary¹²
- continuous arteriovenous hemofiltration (CAVH): adjustment not required⁷

***Children:**

Cycle Length:

Intravenous: 2-4 weeks^{41,42}: 200 mg/m² (range 70-200 mg/m²) IV over 24 hours or divided IV every 12 hours for 5 consecutive days (range 2-10 days) starting on day 1 (total dose per cycle 1,000 mg/m² [range 140-2,000 mg/m²])

High-dose therapy^{41,42}:3,000 mg/m² IV every 12 hours for up to 6 consecutive days starting on day 1 (total dose \leq 36,000 mg/m²)**note: high-dose therapy should only be used by physicians experienced in managing its side effects**

Subcutaneous/Intramuscular: 1-4 weeks⁴¹: 1 mg/kg (range 1-1.5 mg/kg) SC or IM for one dose on day 1 (total dose per cycle 1 mg/kg [range 1-1.5 mg/kg])

Intrathecal: n/a^{6,41}: 30 mg/m² (range 5-75 mg/m²) IT for one dose every 4 days (range 2-7 days) until CSF findings normalize, followed by one additional dose

or

Age (years)	Dose
<1	20 mg
1-2	30 mg
2-3	50 mg
>3	70 mg

The safety and effectiveness of liposomal cytarabine in children has not been established.⁹

*do not use diluents containing benzyl alcohol in neonates²

REFERENCES:

1. McEvoy GK. AHFS 2006 Drug Information. Bethesda, Maryland: American Society of Health-System Pharmacists, Inc.; 2006. p. 1003-1007.
2. Mayne Pharma (Canada) Inc. Cytarabine Injection Product Monograph. Montreal, Quebec; 25 July 2003.
3. MARTINDALE - The Complete Drug Reference (database on the Internet). Cytarabine. Thomson MICROMEDEX®, 2006. Available at: www.micromedex.com. Accessed 21 December 2006.
4. USPDI® Drug Information for the Health Care Professional (database on the Internet). Cytarabine (Systemic). Thomson MICROMEDEX, 2004. Available at: www.micromedex.com. Accessed 5 June 2006.
5. Hamada A, Kawaguchi T, Nakano M. Clinical pharmacokinetics of cytarabine formulations. Clin Pharmacokinet 2002;41(10):705-718.
6. DRUGDEX® Evaluations (database on the Internet). Cytarabine. Thomson MICROMEDEX®, 2006. Available at: www.micromedex.com. Accessed 21 December 2006.

7. Aronoff GR, Berns JS, Brier ME, Golper TA, et al. Drug prescribing in renal failure: dosing guidelines for adults. 4th ed. Philadelphia, Pennsylvania: American College of Physicians; 1999. p. 73.
8. Pizzo P, Poplack D. Principles and Practice of Pediatric Oncology. 5th ed. Philadelphia: Lippincott - Raven; 2006. p. 345-346.
9. USPDI® Drug Information for the Health Care Professional (database on the Internet). Cytarabine, Liposomal (Intrathecal). Thompson MICROMEDEX®, 2006. Available at: www.micromedex.com. Accessed 12 January 2007.
10. Costabile RA. The effects of cancer and cancer therapy on male reproductive function. J Urol 1993;149(5 SUPPL.):1327-1330.
11. John Shepherd MD. Personal communication. BC Cancer Agency Leukemia/BMT Tumour Group; 28 March 2007.
12. Rose BD editor. Cytarabine. www.uptodate.com ed. Waltham, Massachusetts: UpToDate 14.3; 2006.
13. BC Cancer Agency Provincial Systemic Therapy Program. Provincial Systemic Therapy Program Policy III-20: Prevention and Management of Extravasation of Chemotherapy. Vancouver, British Columbia: BC Cancer Agency; 1 September 2006.
14. Pfizer Canada Inc. CYTOSAR® Sterile Powder Product Monograph. Kirkland, Quebec; 17 March 2004.
15. John Shepherd MD. Personal communication. BC Cancer Agency Leukemia/BMT Tumour Group; 28 February 2007.
16. Selkin BA, Savarese DM. Cutaneous complications of chemotherapy. In UpToDate 14.3; Rose, Burton D. (Ed), 2007. Available at: www.uptodate.com. Accessed 30 January 2007.
17. BC Cancer Agency. (SCNAUSEA) Guidelines for Prevention and Treatment of Chemotherapy-induced Nausea and Vomiting in Adults. Vancouver, British Columbia: BC Cancer Agency; 1 November 2005.
18. Briassoulis E, Pavlidis N. Noncardiogenic pulmonary edema: An unusual and serious complication of anticancer therapy. Oncologist 2001;6(2):153-161.
19. Chng WJ. Cytarabine syndrome revisited. Br J of Haematol 2003;122(6):875.
20. Ek T, Abrahamsson J. The paediatric cytarabine syndrome can be viewed as a drug-induced cytokine release syndrome.[comment]. Br J Haematol 2004;124(5):691.
21. BC Cancer Agency Leukemia/BMT Tumour Group. (LYIVACR + R) BCCA PPO for Treatment of Burkitt's Lymphoma and Leukemia LYIVAC (Magrath B) +R (Rituximab). Vancouver: BC Cancer Agency; 1 December 2006.
22. 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):833-9.
23. BC Cancer Agency Leukemia/BMT Tumour Group. (LYIVACR) BCCA Protocol Summary for Treatment of Burkitt's Lymphoma and Leukemia (ALL-L3) with Ifosfamide, Mesna, Etoposide, Cytarabine (IVAC) and Rituximab. Vancouver, British Columbia: BC Cancer Agency; 1 January 2007.
24. Damon LE, Mass R, Linker CA. The association between high-dose cytarabine neurotoxicity and renal insufficiency. J Clin Oncol 1989;7(10):1563-1568.
25. DeVita VT, Hellman S, Rosenberg SA. Cancer Principles & Practice of Oncology. 6th ed. Philadelphia, Pennsylvania: Lippincott Williams & Wilkins; 2001. p. 2640.
26. Leukemia/Bone Marrow Transplant Program of British Columbia. Leukemia/BMT Manual. 4th ed. Vancouver, British Columbia: Vancouver Hospital and Health Sciences Centre / BC Cancer Agency; 2003. p. 27.
27. Sanofi-Synthelabo. FASTURTEC® product information. Markham, Ontario; 2004.
28. Leukemia/Bone Marrow Transplant Program of British Columbia. Leukemia/BMT Manual. E-Edition ed. Vancouver, British Columbia: Vancouver Hospital and Health Sciences Centre / BC Cancer Agency; 2010. p. 93-94.
29. Enzon Inc. DEPOCYT® package insert. Bridgewater, New Jersey; October 2003.
30. Drug Interaction Facts [database on the Internet]. Cytarabine. Facts and Comparisons 4.0, Available at: <http://online.factsandcomparisons.com>, 2006.
31. MARTINDALE - The Complete Drug Reference (database on the Internet). Fludarabine. Thomson MICROMEDEX®, 2006. Available at: www.micromedex.com. Accessed 7 September 2006.
32. McEvoy GK, editor. AHFS 2006 Drug Information. Bethesda, Maryland: American Society of Health-System Pharmacists, Inc. p. 1046-1052.
33. Pfizer Canada Inc. CYTOSAR® product monograph. Kirkland, Quebec; 28 January 2014.
34. Hospira Healthcare Corporation. Cytarabine® injection product monograph. Saint-Laurent, Quebec; 29 July 2009.
35. BC Cancer Agency Miscellaneous Origin Tumour Group. (MOIT) BCCA Protocol Summary for Solid Tumours Using Intrathecal Methotrexate and/or Thiopeta and/or Cytarabine. Vancouver: BC Cancer Agency; 1 July 2005.
36. BC Cancer Agency Lymphoma Tumour Group. (LYIT) BCCA Protocol Summary for Treatment of Lymphoma using Intrathecal Methotrexate and Cytarabine. Vancouver: BC Cancer Agency; 1 September 2006.
37. BC Cancer Agency Leukemia/BMT Tumour Group. (LYCODOXMR) BCCA Protocol Summary for Treatment of Burkitt's Lymphoma and Leukemia (ALL-L3) with Cyclophosphamide, Vincristine, Doxorubicin, Methotrexate, Leucovorin (CODOX-M) and Rituximab. Vancouver: BC Cancer Agency; 1 December 2006.
38. Burnett AK, Milligan D, Prentice AG, et al. A comparison of low-dose cytarabine and hydroxyurea with or without all-trans retinoic acid for acute myeloid leukemia and high risk myelodysplastic syndrome in patients not considered fit for intensive treatment. Cancer 2007;109(6):1114-1124.
39. BC Cancer Agency Leukemia/BMT Tumour Group. (LKAMLCYT) BCCA Protocol Summary for Therapy of Acute Myeloid Leukemia Using Low Dose Cytarabine. Vancouver, British Columbia: BC Cancer Agency; 1 January 2012.
40. Guilhot F, Chastang C, Michallet M, et al. Interferon alfa-2b combined with cytarabine versus interferon alone in chronic myelogenous leukemia. N Engl J Med 1997;337(4):223-229.
41. Rose BD editor. Cytarabine: Pediatric drug information. www.uptodate.com ed. Waltham, Massachusetts: UpToDate 14.3; 2006.
42. Pizzo P, Poplack D. Principles and Practice of Pediatric Oncology. 5th ed. Philadelphia: Lippincott - Raven; 2006. p. 326.