CYTARABINE:

Class: Antineoplastic Agent, Antimetabolite (Pyrimidine Analog)

Indications: - AML induction - AML consolidation -AML salvage treatment
-Acute promyelocytic leukemia (APL) induction APL consolidation
-Acute lymphocytic leukemia -Chronic lymphocytic leukemia
-Chronic myeloid leukemia -CNS lymphoma, primary Hodgkin lymphoma, relapsed or refractory
-Non-Hodgkin's lymphomas -Meningeal leukemia
-*CNS prophylaxis (ALL)* - *Leptomeningeal metastases treatment*:

Available dosage form in the hospital: 100mg vial || 500mg vial ||1g vial

Trade Names: Alexan (AT) , Ara-C ,

Dosage: Details concerning dosing in combination regimens should also be consulted.
-**Acute myeloid leukemia (AML) remission induction:** I.V.: Standard-dose (provided in the FDA-approved labeling): 100 mg/m^2/day continuous infusion for 7 days **or** 200 mg/m^2/day continuous infusion (as 100 mg/m^2 over 12 hours every 12 hours) for 7 days

-**AML induction:** I.V.:

-*7 + 3 regimens (a second induction course may be administered if needed; refer to specific references):* 100 mg/m^2/day continuous infusion for 7 days (in combination with daunorubicin or idarubicin or mitoxantrone) (Arlin, 1990; Dillman, 1991; Fernandez, 2009; Wiernick, 1992) or (Adults <60 years) 200 mg/m^2/day continuous infusion for 7 days (in combination with daunorubicin) (Dillman, 1991)

-*Low intensity therapy (unlabeled dosing):* Adults ≥65 years: SubQ: 20 mg/m^2/day for 14 days out of every 28-day cycle for at least 4 cycles (Fenaux, 2010) or 10 mg/m^2 every 12 hours for 21 days; if complete response not achieved, may repeat a second course after 15 days (Tilly, 1990)

-**AML consolidation (unlabeled use):** I.V.:

-*5 + 2 regimens:* 100 mg/m^2/day continuous infusion for 5 days (in combination with daunorubicin or idarubicin or mitoxantrone) (Arlin, 1990; Wiernick, 1992)

-*5 + 2 + 5 regimen:* 100 mg/m^2/day continuous infusion for 5 days (in combination with daunorubicin and etoposide) (Bishop, 1996)

-*Single-agent:* Adults ≤60 years: 3000 mg/m^2 over 3 hours every 12 hours on days 1, 3, and 5 (total of 6 doses); repeat every 28-35 days for 4 courses (Mayer, 1994)

-**AML salvage treatment (unlabeled use):** I.V.:

-*ADE regimen:* Course 1: 100 mg/m^2 I.V push every 12 hours for 10 days (in combination with daunorubicin and etoposide) followed by Course 2: 100 mg/m^2 I.V push every 12 hours for 8 days (Milligan, 2006)

-*CLAG regimen:* 2000 mg/m^2/day over 4 hours for 5 days (in combination with cladribine and G-CSF); may repeat once if needed (Wrzesień -Kuś, 2003)

-*CLAG-M regimen:* 2000 mg/m^2/day over 4 hours for 5 days (in combination with cladribine, G-CSF, and mitoxantrone); may repeat once if needed (Wierzbowska, 2008)

-*FLAG regimen:* 2000 mg/m^2/day over 4 hours for 5 days (in combination with fludarabine and G-CSF); may repeat once if needed (Montillo, 1998)

-*HiDAC (high-dose cytarabine) ± an anthracycline:* 3000 mg/m^2 over 1 hour every 12 hours for 12 doses (Herzig, 1985)

-*MEC regimen:* 1000 mg/m^2/day over 6 hours for 6 days (in combination with mitoxantrone and etoposide) (Amadori, 1991) or

**Adults <60 years: 500 mg/m^2/day continuous infusion days 1, 2, and 3 and days 8, 9, and 10 (in combination with mitoxantrone and etoposide); may administer a second course if needed (Archimbaud, 1991; Archimbaud, 1995)

-Acute promyelocytic leukemia (APL) induction (unlabeled dosing): I.V.: 200 mg/m^2/day continuous infusion for 7 days beginning on day 3 of treatment (in combination with tretinoin and daunorubicin) (Ades, 2006; Powell, 2010)

-APL consolidation (unlabeled use): I.V.:

-*In combination with idarubicin and tretinoin:* High-risk patients (WBC ≥10,000/mm^3) (Sanz, 2010): Adults ≤60 years:

-First consolidation course: 1000 mg/m^2/day for 4 days

-Third consolidation course: 150 mg/m^2 every 8 hours for 4 days

-*In combination with idarubicin, tretinoin, and thioguanine:* High-risk patients (WBC >10,000/mm^3) (Lo Coco, 2010): Adults ≤61 years:

-First consolidation course: 1000 mg/m^2/day for 4 days

-Third consolidation course: 150 mg/m^2 every 8 hours for 5 days

-*In combination with daunorubicin* (Ades, 2006; Ades, 2008):

-First consolidation course: 200 mg/m^2/day for 7 days

-Second consolidation course:

- Age ≤60 years and low risk (WBC <10,000/mm^3): 1000 mg/m^2 every 12 hours for 4 days (8 doses)
- Age <50 years and high risk (WBC ≥10,000/mm^3): 2000 mg/m^2 every 12 hours for 5 days (10 doses)
- Age 50-60 years and high risk (WBC ≥10,000/mm^3): 1500 mg/m^2 every 12 hours for 5 days (10 doses) (Ades, 2008)
- Age >60 years and high risk (WBC ≥10,000/mm^3): 1000 mg/m^2 every 12 hours for 4 days (8 doses)

-Acute lymphocytic leukemia (ALL; unlabeled dosing):

-*Induction regimen, relapsed or refractory:* I.V.: 3000 mg/m^2 over 3 hours daily for 5 days (in combination with idarubicin [day 3]) (Weiss, 2002)

-*Dose-intensive regimen:* I.V.: 3000 mg/m^2 over 2 hours every 12 hours days 2 and 3 (4 doses/cycle) of even numbered cycles (in combination with methotrexate; alternates with Hyper-CVAD) (Kantarjian, 2000)

-*Larson regimen* (Larson, 1995): SubQ

- Early intensification phase: 75 mg/m^2/dose days 1 to 4 and 8 to 11 (4-week cycle; repeat once)
- Late intensification phase: 75 mg/m^2/dose days 29 to 32 and 36 to 39

-*Linker protocol:* I.V.: 300 mg/m^2/day days 1, 4, 8, and 11 of even numbered consolidation cycles (in combination with teniposide) (Linker, 1991)

-Chronic lymphocytic leukemia (CLL; unlabeled use):

OFAR regimen: I.V.: 1000 mg/m^2/dose over 2 hours days 2 and 3 every 4 weeks for up to 6 cycles (in combination with oxaliplatin, fludarabine, and rituximab) (Tsimberidou, 2008)

-**Chronic myeloid leukemia (CML; unlabeled dosing):** SubQ: 20 mg/m^2/dose days 15 to 24 every month (in combination with interferon alfa-2b) (Guilhot, 1997)

-**CNS lymphoma, primary (unlabeled use):** I.V.: 2000 mg/m^2 over 1 hour every 12 hours days 2 and 3 (total of 4 doses) every 3 weeks (in combination with methotrexate and followed by whole brain irradiation) for a total of 4 courses (Ferreri, 2009)

-**Hodgkin lymphoma, relapsed or refractory (unlabeled use):** I.V.:

-*DHAP regimen:* 2000 mg/m^2 over 3 hours every 12 hours day 2 (total of 2 doses/cycle) for 2 cycles (in combination with dexamethasone and cisplatin) (Josting, 2002)

-*ESHAP regimen:* 2000 mg/m^2 day 5 (in combination with etoposide, methylprednisolone, and cisplatin) every 3 to 4 weeks for 3 or 6 cycles (Aparicio, 1999)

-*Mini-BEAM regimen:* 100 mg/m^2 every 12 hours days 2 to 5 (total of 8 doses) every 4-6 weeks (in combination with carmustine, etoposide, and melphalan) (Colwill, 1995; Martin, 2001)

-*BEAM regimen (transplant preparative regimen):* 200 mg/m^2 twice daily for 4 days beginning 5 days prior to transplant (in combination with carmustine, etoposide, and melphalan) (Chopra, 1993)

-**Non-Hodgkin's lymphomas (unlabeled use):** I.V.:

-*CALGB 9251 regimen:* Cycles 2, 4, and 6: 150 mg/m^2/day continuous infusion days 4 and 5 (Lee, 2001; Rizzieri, 2004)

-*CODOX-M/IVAC regimen:*

- Adults ≤60 years: Cycles 2 and 4 (IVAC): 2000 mg/m^2 every 12 hours days 1 and 2 (total of 4 doses/cycle) (IVAC is combination with ifosfamide, mesna, and etoposide; IVAC alternates with CODOX-M) (Magrath, 1996)
- Adults ≤65 years: Cycles 2 and 4 (IVAC): 2000 mg/m^2 over 3 hours every 12 hours days 1 and 2 (total of 4 doses/cycle) (IVAC is combination with ifosfamide, mesna, and etoposide; IVAC alternates with CODOX-M) (Mead, 2008)
- Adults >65 years: Cycles 2 and 4 (IVAC): 1000 mg/m^2 over 3 hours every 12 hours days 1 and 2 (total of 4 doses/cycle) (IVAC is combination with ifosfamide, mesna, and etoposide; IVAC alternates with CODOX-M) (Mead, 2008)

-*DHAP regimen:*

- Adults ≤70 years: 2000 mg/m^2 over 3 hours every 12 hours day 2 (total of 2 doses/cycle) every 3-4 weeks for 6-10 cycles (in combination with dexamethasone and cisplatin) (Velasquez, 1988)
- Adults >70 years: 1000 mg/m^2 over 3 hours every 12 hours day 2 (total of 2 doses/cycle) every 3-4 weeks for 6-10 cycles (in combination with dexamethasone and cisplatin) (Velasquez, 1988)

-*ESHAP regimen:* 2000 mg/m^2 over 2 hours day 5 every 3-4 weeks for 6-8 cycles (in combination with etoposide, methylprednisolone, and cisplatin) (Velasquez, 1994)

-*BEAM regimen (transplant preparative regimen):* 200 mg/m^2 twice daily for 3 days beginning 4 days prior to transplant (in combination with carmustine, etoposide, and melphalan) (Linch 2010) or 100 mg/m^2 over 1 hour every 12 hours for 4 days beginning 5 days prior to transplant (in combination with carmustine, etoposide, and melphalan) (van Imhoff, 2005)

-**Meningeal leukemia**: I.T.: **Note**: Optimal intrathecal chemotherapy dosing should be based on age rather than on body surface area (BSA); CSF volume correlates with age and not to BSA (Bleyer, 1983; Kerr, 2001). Dosing provided in the FDA-approved labeling is BSA-based (usual dose 30 mg/m^2 every 4 days; range: 5-75 mg/m^{2}once daily for 4 days or once every 4 days until CNS findings normalize, followed by 1 additional treatment).

-**Unlabeled uses or doses for intrathecal therapy:** I.T.:

-*CNS prophylaxis (ALL):* 100 mg weekly for 8 doses, then every 2 weeks for 8 doses, then monthly for 6 doses (high-risk patients) or 100 mg on day 7 or 8 with each chemotherapy cycle for 4 doses (low risk patients) or 16 doses (high-risk patients) (Cortes, 1995)

or as part of intrathecal triple therapy (TIT): 40 mg days 0 and 14 during induction, days 1, 4, 8, and 11 during CNS therapy phase, every 18 weeks during intensification and maintenance phases (Storring, 2009)

-*CNS prophylaxis (APL, as part of TIT):* 50 mg per dose; administer 1 dose prior to consolidation and 2 doses during each of 2 consolidation phases (total of 5 doses) (Ades, 2006; Ades, 2008)

-*CNS leukemia treatment (ALL, as part of TIT):* 40 mg twice weekly until CSF cleared (Storring, 2009)

-*CNS lymphoma treatment:* 50 mg twice a week for 4 weeks, then weekly for 4-8 weeks, then every other week for 4 weeks, then every 4 weeks for 4 doses (Glantz, 1999)

-*Leptomeningeal metastases treatment*: 50 mg twice a week for 4 weeks, then weekly for 4 weeks then monthly for 4 doses (NCCN CNS cancer guidelines v.1.2010) or40-60 mg per dose (DeAngelis, 2005).

Geriatric

Refer to adult dosing.

Renal Impairment:

The FDA-approved labeling does not contain renal dosing adjustment guidelines; the following guidelines have been used by some clinicians:

-Aronoff, 2007 (cytarabine 100-200 mg/m^2): Children and Adults: No adjustment necessary

-Kintzel, 1995 (high-dose cytarabine 1-3 g/m^2):

- Cl_{cr} 46-60 mL/minute: Administer 60% of dose
- Cl_{cr} 31-45 mL/minute: Administer 50% of dose
- Cl_{cr} <30 mL/minute: Consider use of alternative drug

-Smith, 1997 (high-dose cytarabine; ≥2 g/m^2/dose):

- Serum creatinine 1.5-1.9 mg/dL or increase (from baseline) of 0.5-1.2 mg/dL: Reduce dose to 1 g/m^2/dose
- Serum creatinine ≥2 mg/dL or increase (from baseline) of >1.2 mg/dL: Reduce dose to 0.1 g/m^2/day as a continuous infusion

-Hemodialysis: In 4 hour dialysis sessions (with high flow polysulfone membrane) 6 hours after cytarabine 1 g/m^2 over 2 hours, 63% of the metabolite ARA-U was extracted from plasma (based on a single adult case report) (Radeski, 2011)

Hepatic Impairment:

-Dose may need to be adjusted in patients with liver failure since cytarabine is partially detoxified in the liver. The FDA-approved labeling does not contain hepatic dosing adjustment guidelines; the following guideline has been used by some clinicians:

-Floyd, 2006: Transaminases (any elevation): Administer 50% of dose; may increase subsequent doses in the absence of toxicities

-Koren, 1992 (dose level not specified): Bilirubin >2 mg/dL: Administer 50% of dose; may increase subsequent doses in the absence of toxicities

Dosing: Obesity

ASCO Guidelines for appropriate chemotherapy dosing in obese adults with cancer: Utilize patient's actual body weight (full weight) for calculation of body surface area- or weight-based dosing, particularly when the intent of therapy is curative; manage regimen-related toxicities in the same manner as for nonobese patients; if a dose reduction is utilized due to toxicity, consider resumption

of full weight-based dosing with subsequent cycles, especially if cause of toxicity (eg, hepatic or renal impairment) is resolved (Griggs, 2012).

Common side effect:

Central nervous system: Fever

Dermatologic: Rash

Gastrointestinal: Anal inflammation, anal ulceration, anorexia, diarrhea, mucositis, nausea, vomiting

Hematologic: Myelosuppression, neutropenia (onset: 1-7 days; nadir [biphasic]: 7-9 days and at 15-24 days; recovery [biphasic]: 9-12 days and at 24-34 days), thrombocytopenia (onset: 5 days; nadir: 12-15 days; recovery 15-25 days), anemia, bleeding, leukopenia, megaloblastosis, reticulocytes decreased

Hepatic: Hepatic dysfunction, transaminases increased (acute)

Local: Thrombophlebitis

Adverse events associated with high-dose cytarabine (CNS, gastrointestinal, ocular, and pulmonary toxicities are more common with high-dose regimens):

Cardiovascular: Cardiomegaly, cardiomyopathy (in combination with cyclophosphamide)

Central nervous system: Cerebellar toxicity, coma, neurotoxicity (up to 55% in patients with renal impairment), personality change, somnolence

Dermatologic: Alopecia (complete), desquamation, rash (severe)

Gastrointestinal: Gastrointestinal ulcer, pancreatitis, peritonitis, pneumatosis cystoides intestinalis

Hepatic: Hyperbilirubinemia, liver abscess, liver damage, necrotizing colitis

Neuromuscular & skeletal: Peripheral neuropathy (motor and sensory)

Ocular: Corneal toxicity, hemorrhagic conjunctivitis

Respiratory: Pulmonary edema, syndrome of sudden respiratory distress

Miscellaneous: Sepsis

Adverse events associated with intrathecal cytarabine administration:

Central nervous system: Accessory nerve paralysis, fever, necrotizing leukoencephalopathy (with concurrent cranial irradiation, I.T. methotrexate, and I.T. hydrocortisone), neurotoxicity, paraplegia

Gastrointestinal: Dysphagia, nausea, vomiting

Ocular: Blindness (with concurrent systemic chemotherapy and cranial irradiation), diplopia

Respiratory: Cough, hoarseness

Miscellaneous: Aphonia

Pregnancy Risk Factor: D