Cytarabine

Cytarabine (cytosine arabinoside) is an analogue of 2'-deoxycytidine that inhibits DNA polymerase activity after being incorporated into DNA as a fraudulent nucleotide, resulting in impaired DNA synthesis.

From: Pharmacology and Therapeutics for Dentistry (Seventh Edition), 2017

Related terms:

Methotrexate, Intrathecal, Cyclophosphamide, Chemotherapy, Etoposide, Vincristine, Seizure, Proteome, DNA

Drug-Induced Pulmonary Disease

V. Courtney Broaddus MD, in Murray & Nadel's Textbook of Respiratory Medicine, 2022

Cytosine Arabinoside

Cytosine arabinoside (ara-C) is a cytotoxic agent used to induce remission in acute leukemia and other hematologic malignant diseases before bone marrow transplantation. Intensive ara-C treatment regimens have been associated with rapidly fatal noncardiogenic pulmonary edema (Fig. 99.3).[5] Histologic examination of lung tissue during ara-C pulmonary toxicity reveals substantial accumulation of intra-alveolar proteinaceous material without the cellular atypia and mononuclear infiltration described with other cytotoxic drugs. In two large series, 13–28% of the patients with toxicity developed respiratory distresswith administration of the drug. The mechanism underlying this reaction is unknown, and the associated mortality is high. Treatment for ara-C pulmonary toxicity is largely supportive.

Cytarabine

Barbara J. Rider, in xPharm: The Comprehensive Pharmacology Reference, 2007

Cytarabine; Cytosar-U (trade); Tarabine (trade); alcysten; alexan; 4 amino 1arabinofuranosyl 1,2 dihydro 2 pyrimidinone; arabinocytosil; arabinofuranosylcytoside; 1 arabinofuranosyl cytosine; arabinofuranosyl cytosine; arabinofuranosylcytosine; arabinoside c; arabinoside cytosine; arabinosinecytosine; arabinosyl cytosine; arabinosylcytosine; arabinosyl cytosinenucleoside; arabinosylcytosine nucleoside; ara C; aracytidine; aracytin; aracytine; 1 beta arabinofuranosylcytosine; 1beta arabinofuranosylcytosine; beta arabinofuranosylcytosine; 1 beta arabinofuranosylcytosine hydrochloride; 1beta arabinofuranosylcytosine hydrochloride; beta arabinofuranosylcytosinehydrochloride; 1 beta arabinosylcytosine; 1beta arabinosylcytosine; betaarabinosylcytosine; beta ara c; 1 (beta d arabinofuranosyl)cytosine; 1 beta darabinofuranosyl cytosine; 1 beta d arabinofuranosylcytosine; 1beta darabinofuranosyl cytosine; 1beta d arabinofuranosylcytosine; 7 beta darabinofuranosylcytosine; beta d arabino furanosyl 1 cytosine; beta darabinofuranosyl1cytosine; 1 beta d arabinofuranosylcytosine hydrochloride; 1(beta d arabinosyl)cytosine; 1 beta d arabinosylcytosine; 1 beta dextroarabinofuranosylcytosine; 7 beta dextro

arabinofuranosylcytosine; 1 betadextro arabinosyl cytosine; citarabine; cyclocide; cylocide; cystosinearabinoside; cytarabide; cytarabin; cytarabine hydrochloride; cytarabinoside; cytarbine; cytidine arabinoside; cytoarabine; cytosar; cytosar 4; cytosar u; cytosin arabinoside; cytosine arabinase; cytosine arabinofuranoside; cytosinearabinonucleoside; cytosine arabinose; cytosine arabinoside; cytosinearabinosine; cytosine beta arabinofuranoside; cytosine beta arabinoside; cytosine beta d arabinofuranoside; cytovis; depocyt; dtc 101; nsc 63878; u19920 a; udicil; 1 (beta d arabinosyl)cytosine; 1 beta d arabinofuranosyl cytosine; 1 beta dextro arabinofuranosylcytosine; 1 beta dextro arabinosyl cytosine; 1beta d arabinofuranosyl cytosine; 4 amino 1 arabinofuranosyl 1,2 dihydro 2 pyrimidinone; 7 beta d arabinofuranosylcytosine; arabinofuranosyl cytoside; arabinosine cytosine; arabinosyl cytosine nucleoside; beta arabinofuranosylcytosine hydrochloride; beta arabinosylcytosine; beta d arabinofuranosyl1cytosine; cystosine arabinoside; cytosine arabinonucleoside; cytosine arabinosine; depocyte; dtc101; nsc63878; u 19920 a; u 19920a; u19920a

Read full chapter

URL: https://www.sciencedirect.com/science/article/pii/B9780080552323615363

Cytarabine

J.K. Aronson MA, DPhil, MBChB, FRCP, HonFBPhS, HonFFPM, in Meyler's Side Effects of Drugs, 2016

Nervous system

Central nervous system disturbances, especially impaired cerebellar function, limit doses of cytarabine, and age is an important predictive factor. Of 418 patients who received 36–48 g/m^2 only 35 (8%) had severe cerebellar toxicity, which was irreversible or fatal in 4 (1%) [2]. Patients over 50 years of age were significantly more likely to develop cerebellar problems than younger patients (26/137, 19%, compared with 9/281, 3%); a second course did not increase the incidence, implying that it is the individual rather than the cumulative dose that is important.

The cerebellar syndrome is the most common complication of high-dose cytarabine therapy. In a study of the cerebellar syndrome caused by cytarabine [3], in which it was found in seven of 30 patients treated, symptoms of toxicity appeared between the third and seventh days of chemotherapy, manifesting first as lethargy and confusion [3]. Within the next 24 hours there were signs of cerebellar dysfunction, including dysarthria, ataxia, tremor, nystagmus, and dysmetria. In most patients in whom neurotoxicity developed, liver function worsened during chemotherapy. Abnormal liver function at the start of therapy and the development of neurotoxicity appear to be linked. The symptoms of neurotoxicity resolved within 4–49 days.

Aseptic meningitis can also occur in patients given cytarabine [4,5], and signs of cerebellar dysfunction after the administration of cytarabine 24 g/m^2 have been reported in association with aseptic meningitis [6].

Cytarabine

Hussein I. El-Subbagh, Abdullah A. Al-Badr, in Profiles of Drug Substances, Excipients and Related Methodology, 2009

1.1.3.1 Cytarabine

Alexan®, Arabine®, Arabitin®, Ara-C®, Ara-Cell®, Aracytin®, Aracytin®, Aracytine®, Arafcyt®, Citagenin®, Citarabina Filaxis®, Citarabina Martian®, Citarabina®, Cyclocide®, Cycloside®, Cytarabel®, Cytarabin®, Cytarabina®, Cytarabine Injection®, Cytarabine®, Cytarabinum Delta West®, Cytonal®, Cytosar®, Cytosar-U®, Cytovis®, Cytozar®, Depocyt®, Erpalfa®, Iretin®, Laracit®, Tarabine PFS®.Tarabine®, Udicil®. [1–7]

Read full chapter

URL: https://www.sciencedirect.com/science/article/pii/S1871512509340029

Acute Myeloid Leukemia

Fred F. Ferri MD, FACP, in Ferri's Clinical Advisor 2022, 2022

Acute General Rx

- The general approach to AML is summarized inFig. 3. Therapy of AML typically has three components:
    1. Immediate therapy to correct metabolic, infectious, or hyperleukocytic emergencies (if needed). Therapy for AML is always urgent but not always an emergency. However, treatment for APML should be considered a medical emergency to prevent catastrophic bleeding.
    2. Induction therapy, which is therapy of active disease intended to obtain remission and restore normal bone marrow function. Remission is defined as blasts <5% in the bone marrow, absolute neutrophils (ANC) of >1000/mcl, platelets >100,000/mcl, and transfusion independence. Complete remission with incomplete marrow recovery (CRi) indicates absence of leukemic blasts in the marrow but persistent cytopenias.
    3. Consolidation therapy, typically some form of intensive chemotherapy or stemcell transplant therapy intended to prevent relapse.
    4. Hyperleukocytic symptoms are typically seen with WBC >100,000/ml. Leukapheresis requires catheter placement and pheresis but spares tumor lysis. Rapid cytoreduction with chemotherapy (hydroxyurea 3 to 6 g orally or cytarabine) is often adequate and easier but risks tumor lysis. Optimal management is therefore individualized.
    5. Tumor lysis syndrome (TLS) is associated with a rise in uric acid, potassium, and serum phosphate, the last causing a reciprocal fall in calcium. The metabolic changes may result in renal failure, cardiac dysrhythmias, muscle spasms (due to low calcium), seizures, and death (a more detailed discussion is in the section on acute lymphocytic leukemia).
    6. The mainstays of therapy for AML are medications dating from the 1970s —daunorubicin and cytarabine—with few medications having meaningful impact on therapy in the last four decades. In 2017, the U.S. FDA approved four new agents, including three targeted agents, for treatment of AML. The role of these agents and their relation to standard therapy is outlined below.
    7. Induction chemotherapy typically consists of daunorubicin 60 or 90 mg/m^2 IV for 3 days and cytarabine (Ara-C) 100 or 200 mg/m^2/day as continuous infusion for 7 days (“7+3”). Success rates are 60% to 80% and have been better in recent trials. Other agents that are used include etoposide, idarubicin, fludarabine, and cladribine. Bone marrow examination is usually performed at day 14 of therapy to assess the response.
    8. Gemtuzumab ozogamicin (GO, Mylotarg) is an antibody-drug conjugate binding an anti-CD33 antibody to the chemotherapeutic agent calicheamicin that was approved in 2017 for therapy of newly diagnosed CD33+ AML. In newly diagnosed AML, the use of low-dose GO when added to standard 7+3 induction had a success rate of 81%, with 2-yr relapse-free survival improving from 22.7% to 50.3% compared with standard therapy alone. The benefit was seen in favorable and intermediate-risk patients.
    9. Midostaurin was also approved in 2017 for treatment of newly diagnosed AML with mutations in the fms-related tyrosine kinase 3*(FLT3)* gene in combination with standard induction therapy. Four-yr overall survival was 51.4% in FLT3-positive patients receiving midostaurin vs. 44.3% in the

placebo arm, with improved durability of remissions in patients achieving remission. The optimal use of these therapies requires rapidaccess to genetic data at the time of diagnosis. Also approved in 2017 was CPX-351, a liposomal formulation of cytarabine and daunorubicin encapsulated in a 5:1 ratio, for patients with AML related to previous therapy (t-AML) or with AML with myelodysplasia-related change (AML-MRC). In a trial of t-AML and AML evolving from myelodysplasia or with WHO-defined myelodysplasia-related cytogenetic changes in patients ages 60 to 75 yr, CPX-351 improved survival to 9.56 mo vs. 5.95 mo with standard 7+3 induction. This overall survival was maintained out to 5 yr (18% vs. 8%).

10. Gilteritinib was FDA approved in 2018 for treatment of adult patients who have relapsed or refractory acute myeloid leukemia with a FLT3 mutation. Approval was based on an interim analysis of a trial, which included 138 adult patients with relapsed or refractory AML having an FLT3 ITD, D835, or I836 mutation. Gilteritinib was given orally at a dose of 120 mg daily until unacceptable toxicity or lack of clinical benefit. After a median follow-up of 4.6 mo, 21% of patients achieved complete remission (CR) or CR with partial hematologic recovery (CRh).
11. In 2018, the FDA granted accelerated approval to venetoclax, a BCL-2 inhibitor, in combination with azacitidine or decitabine or low-dose cytarabine for the treatment of newly diagnosed acute myeloid leukemia in adults who are age 75 yr or older, or who have comorbidities that preclude the use of intensive induction chemotherapy. The recommended venetoclax dose depends upon the combination regimen.

- Consolidation therapy is controversial. For patients managed with chemotherapy, cytarabine 3 g/m^2 for six doses is commonly used (day 1, 3, 5), but intermediate doses (1000-1500 mg/m^2) for six doses appear equally effective and less toxic. Doses above 1000 mg/m^2 are poorly tolerated in patients over 60 yr because of cerebellar toxicity. Renal insufficiency also increases the risk of cerebellar toxicity from Ara-C, which can be severe.
    1. For favorable risk disease, consolidation with chemotherapy alone with two to four cycles of intermediate/high-dose cytarabine is typically given, with long-term survival of 60% to 70%.
    2. For intermediate-risk and unfavorable-risk disease, first-remission allogeneic stem cell marrow transplant is often recommended if a donor is available. If not, chemotherapy consolidation chemotherapy is offered, although the optimal therapy and schedule, especially for unfavorable disease, is uncertain.
    3. In the trial of GO as initial therapy, GO was also used in consolidation with high-dose cytarabine and daunorubicin.
    4. The role of autologous bone marrow transplant is controversial, with some evidence of decreased relapse rates after chemotherapy but no clear benefit in overall survival.
    5. Allogeneic bone marrow transplant is offered to patients with relapsed disease if a second remission can be obtained in good-risk patients. It is offered to high-risk and intermediate-risk patients in first remission if a donor is available. In 2018, most patients will be able to find a donor from either a matched related donor, matched unrelated donor, mismatched unrelated donor, haploidentical donor, or cord blood donor. The Center for International Blood and Marrow Transplant Research (CIBMTR) has published data for 12,309 patients receiving an HLA-matched sibling transplant and 15,632 patients receiving a matched unrelated donor for AML between 2002 and 2012. Their disease status at the time of transplant and the donor type were found to be the best predictors of posttransplant survival. The 3-yr probabilities of survival after HLA-matched sibling transplant in this cohort was 58% ± 1%, 50% ± 1%, and 24% ± 1% for patients with early, intermediate, and advanced disease, respectively. The probabilities of survival after an unrelated donor

transplant were 49% ± 1%, 47% ± 1%, and 22% ± 1% for patient with early, intermediate, and advanced disease, respectively.

6. Enasidenib, a selective inhibitor of mutated isocitrate dehydrogenase 2 (IDH-2), was approved by the FDA in 2017 for relapsed or refractory AML with IDH-2 mutations. IDH-2 mutations are found in about 12% of AML patients. At a dose of 100 mg orally, the response rate was 40.3%, with 19.3% achieving remission, some durable. Differentiation syndrome can be seen with enasidenib, similar to therapy for APML. In November 2020, results of the phase 3 IDHENTIFY study for relapsed or refractory AML failed to meet the primary endpoint of overall survival. This study compared enasidenib and best supportive care to conventional care regimens, including best supportive care only, azacitidine and best supportive, low-dose cytarabine and best supportive care, or intermediate-dose cytarabine and best supportive care.
7. Ivosidenib, a selective inhibitor of isocitrate dehydrogenase-1 (IDH-1) mutation, was approved by the FDA in 2018 as the first treatment of adult patients with relapsed/refractory acute myeloid leukemia with an IDH-1 mutation. Approval was based on results from a phase 1, open-label, single-arm, multicenter, dose-escalation, expansion trial of adult patients in this population. The primary end point was combined complete remission and complete remission with partial hematologic improvement; the combined rate was 32.8%,and the median duration of remission was 8.2 mo.
8. Relapses after bone marrow transplant can sometimes be managed with donor lymphocyte infusions, adjustment of immune suppression, and chemotherapy (often low intensity). In general, outcomes are poor with posttransplant relapses.

- Treatment of older patients (>60 yr) is problematic, with cure rates of 10% to 15%. Older patients do worse because they are more likely to have high-risk features and less likely to tolerate therapy. Several models have been devised to identify variables that predict which patients may do well with conventional therapy versus those who will not (Table 7). Options for these patients include:
  1. Standard induction therapy is reasonable for patients likely to tolerate it. Even in the absence of cure, quality of life is often excellent in remission. More recent studies suggest that the early death rate (within 30 days of diagnosis) was lower for patients in their 70s and 80s receiving standard induction. There is no standardized approach to evaluating fitness for therapy; one algorithm is atwww.aml-score.org/.
  2. Hypomethylating agents—decitabine and azacytidine—may be considered in patients unlikely to tolerate induction therapy. Azacytidine (75 mg/m^2 daily for 7 days every 28 days) and decitabine (20 mg/m^2 for 5 days every 28 days) are considered in older patients who are not considered appropriate for induction chemotherapy. Both are outpatient regimens, and decitabine especially is very well tolerated. Recent data with azacytidine suggest benefit in about 20% to 30% lasting 14 to 16 mo in responders, with equivalent results in low blast count (20%-30% in the bone marrow) vs. higher blast count disease.
  3. Single-agent gemtuzumab ozogamicin is an option for treatment of CD33+ AML in patients considered unfit for induction. The benefit compared to best supportive care (BSC) was mainly seen in patients with CD33 expression of greater than 80% and favorable/intermediate cytogenetics (1 yr survival 22% and 37% respectively, BSC <10%), with no benefit in patients with high-risk cytogenetics.
  4. Low-dose cytarabine 20 mg/m^2 twice daily or 40 mg/m^2 daily for 10 days subcutaneously) has shown survival benefit over hydroxyurea in low-/intermediate- risk patients.
  5. In November 2018, the FDA granted the accelerated approval to venetoclax (a bcl-2 protein inhibitor) in combination with azacitidine or

decitabine or low-dose cytarabine for the treatment of newly diagnosed acute myeloid leukemia in adults who are age 75 yr or older, or who have comorbidities that preclude use of intensive induction chemotherapy. The recommended venetoclax dose depends upon the combination regimen and is described in prescribing information of venetoclax.

6. In November 2018, the FDA approved glasdegib (a small molecule inhibitor of Sonic hedgehog pathway) in combination with low-dose cytarabine (LDAC), for newly diagnosed acute myeloid leukemia in patients who are 75 yr old or older or who have comorbidities that preclude intensive induction chemotherapy. Approval was based upon a multicenter, open-label, randomized study that randomized eligible patients 2:1 to receive glasdegib, 100 mg daily, with LDAC 20 mg subcutaneously twice daily on days 1 to 10 of a 28-day cycle or LDAC alone in 28-day cycles until disease progression or unacceptable toxicity. Efficacy was established based on an improvement in overall survival, 8.3 mo for LDAC + glasdegib versus 4.3 mo for LDAC alone. HR of 0.46 (95% CI: 0.30, 0.71; p=0.0002).
7. Oral hydroxyurea dosed to counts and cytopenias.
8. Best supportive care.
9. Reduced-intensity allogeneic stem cell transplant is an option for patients in remission after standard therapy. A recent meta-analysis of studies including 749 patients over 60 receiving RIT identified a 3-yr relapse-free survival of 35%.

- **Acute Promyelocytic Leukemia (APML):** APML is a distinct leukemia syndrome with very different treatment implications. Cure rates greater than 95% have been seen in current protocols in the absence of high-risk features. It is associated with t(15;17), which translocates the PML gene to retinoic acid receptor α (PML-RARa). Uncommon variants are t(11;17) and t(5;17). Risk groups for relapse were defined in studies using retinoic acid and chemotherapy. Patients with presenting WBC >10,000/mcl were considered highrisk, patients with WBC ≤10,000 and platelets >40,000 were considered low risk, and all others were considered intermediate risk. In current protocols, high-risk patients receive some form of intensified therapy.
- APML is a medical emergency because of the high risk of bleeding complications.
    1. All patients with APML have DIC, caused by overexpression of annexin II (which increases generation of plasmin, degrading fibrin), elastases (which degrade fibrinogen and fibrinolytic inhibitors), and increased endothelial tissue plasminogen activator release.
    2. Early death due to hemorrhage is seen in 5% to 17% of newly diagnosed APML patients, usually intracranial or pulmonary. Risk factors include elevated WBC, increased age, and elevated creatinine.
    3. Retinoic acid rapidly stabilizes the coagulopathy of APML; consideration should be given to starting this immediately for suspected cases.
    4. Cryoprecipitate (usual dose 10 bags) to raise the fibrinogen level to 150 mg/dl and platelet transfusion to raise the count to >50,000mcl should be given as needed.
    5. Unfractionated heparin may paradoxically stop bleeding in APML by inhibiting DIC, but is rarely used in the retinoic acid treatment era.
- Diagnosis of APML.
    1. Rapid diagnosis is essential due to treatment implications.
    2. Diagnosis by classic APML blast morphology and clinical syndrome (especially DIC with low fibrinogen) is sufficient to justify starting treatment with retinoic acid pending confirmation with molecular studies. Immediate therapy with retinoic acid will rapidly stabilize the coagulopathy and help prevent catastrophic bleeding.

3. Polymerase chain reaction for PML/RARa.
4. FISH for t(15;17) or variants.
5. Flow cytometry is typically distinct with lack of HLA-DR and CD34; CD13, CD33 and CD64 are usually positive.

- Therapy of APML.
  1. Emergency measures to stabilize coagulopathy as outlined previously.
  2. Patients with WBC ≤10,000 (low/intermediate risk) are treated with retinoic acid and arsenic trioxide ("differentiation therapy").
  3. Therapy of high-risk patients is less well standardized but has included intensification with cytarabine, anthracyclines, and gemtuzumab ozogamicin. A recent trial using arsenic and retinoic acid with GO demonstrated 100% 4-yr survival in high-risk patients after 30 days, emphasizing the importance of preventing early deaths in APML.
  4. Maintenance therapy for 2 yr is given in some APML protocols.
  5. Patients with high-risk disease receive central nervous system prophylaxis with intrathecal chemotherapy.
  6. Treatment of relapsed disease typically consists of autologous bone marrow transplant after obtaining second remission.
- Differentiation syndrome (DS) is a potentially fatal complication of therapy with retinoic acid and arsenic trioxide. It is associated with fever, interstitial pulmonary infiltrates, peripheral edema, pleural and pericardial effusions and renal failure; it is commonly associated with rising WBC seen in patients on differentiation therapy.
  1. Therapy for suspected differentiation syndrome is dexamethasone 10 mg/m^2 every 12 hr. Cytoreductive therapy (hydroxyurea, idarubicin) and stopping retinoic acid and arsenic are appropriate for inadequate response to dexamethasone.
  2. Prophylaxis for differentiation syndrome with dexamethasone 2.5 mg/m^2 every 12 hr has been suggested for WBC >5000 or creatinine >1.4 mg/dl. Hydroxyurea is used to keep the WBC below 10,000/mcl in some protocols.

Cytarabine

In Meyler's Side Effects of Drugs (Sixteenth Edition), 2016

Nervous system

Central nervous system disturbances, especially impaired cerebellar function, limit doses of cytarabine, and age is an important predictive factor. Of 418 patients who received 36–48 g/m^2 only 35 (8%) had severe cerebellar toxicity, which was irreversible or fatal in 4 (1%) [2]. Patients over 50 years of age were significantly more likely to develop cerebellar problems than younger patients (26/137, 19%, compared with 9/281, 3%); a second course did not increase the incidence, implying that it is the individual rather than the cumulative dose that is important.

The cerebellar syndrome is the most common complication of high-dose cytarabine therapy. In a study of the cerebellar syndrome caused by cytarabine [3], in which it was found in seven of 30 patients treated, symptoms of toxicity appeared between the third and seventh days of chemotherapy, manifesting first as lethargy and confusion [3]. Within the next 24 hours there were signs of cerebellar dysfunction, including dysarthria, ataxia, tremor, nystagmus, and dysmetria. In most patients in whom neurotoxicity developed, liver function worsened during chemotherapy. Abnormal liver function at the start of therapy and the development of neurotoxicity appear to be linked. The symptoms of neurotoxicity resolved within 4–49 days.

Aseptic meningitis can also occur in patients given cytarabine [4,5], and signs of cerebellar dysfunction after the administration of cytarabine 24 g/m^2 have been reported in association with aseptic meningitis [6].

Read full chapter

URL: https://www.sciencedirect.com/science/article/pii/B9780444537171005771

NEUROLOGICAL COMPLICATIONS OF CANCER TREATMENTS

William Whiteley, Robin Grant, in Neurology and Clinical Neuroscience, 2007

Cytosine Arabinoside

Cytosine arabinoside (Ara-C or cytarabine) is used for hematological malignancies, breast cancer, and occasionally is given intrathecally for leptomeningeal carcinomatosis. High-dose Ara-C causes a reversible cerebellar syndrome in 10% to 20% of patients. It usually starts a few days after treatment, peaks at 2 to 3 days, and then resolves within 2 weeks of treatment, although the resolution may be incomplete. Occasionally, a more diffuse encephalopathy occurs with seizures. Intrathecal therapy can lead to a chemical meningitis and myelopathy. Neuropathy is rarely reported, especially where Ara-C is used with other drugs.

Read full chapter

URL: https://www.sciencedirect.com/science/article/pii/B9780323033541501048

Pyrimidine Antimetabolites☆

B.B. FreemanIII, G. Pizzorno, in Reference Module in Biomedical Sciences, 2014

Therapeutic Uses

Cytarabine is indicated for remission induction in patients with acute myelocytic leukemia. It is more effective when it is combined with anthracyclines. Low-dose Ara-C is used in the treatment of chronic myelogenous leukemia in combination with interferon-α.

It is also active against acute lymphocytic leukemia and may be used for the treatment of relapses of acute lymphocytic leukemia in both children and adults. In combination with other agents, Ara-C is used in the treatment of non-Hodgkin lymphomas. Ara-C is not particularly useful in the treatment of solid tumors.

Read full chapter

URL: https://www.sciencedirect.com/science/article/pii/B9780128012383044299

Pharmacology and Molecular Mechanisms of Antineoplastic Agents for Hematologic Malignancies

Stanton L. Gerson, ... Richard J. Creger, in Hematology (Seventh Edition), 2018

Chemistry and Mechanism of Action:

Cytosine arabinoside (1′-β-d-arabinofuranosylcytosine; ara-C) is a nucleoside analog that differs from its naturally occurring counterpart (2′-deoxycytidine) by virtue of the presence of a hydroxyl group in the 2′-β configuration. The altered reactivity of the resulting arabinosyl sugar moiety confers on ara-C its cytotoxic activity. Ara-C enters the cell by a facilitated nucleoside diffusion mechanism and is converted to its nucleoside monophosphate form, ara-CMP, by the pyrimidine salvage pathway enzyme, deoxycytidine kinase. This represents the rate-limiting step in ara-C metabolism. Ara-C may also be catabolized intracellularly to an inactive form, ara-U, by the enzyme cytidine deaminase (CDD). Ara-C is ultimately converted to its lethal triphosphate derivative, ara-CTP, by a mono- and diphosphate kinase. Ara-CTP is an inhibitor of DNA polymerases α, β, and γ, and is

also incorporated into replicating DNA strands, leading to inhibition of chain initiation and elongation and premature chain termination. The extent of incorporation of ara-C into DNA closely correlates with lethality in leukemic cells. Although ara-C is generally thought of as a prototypical S-phase–specific agent, its ability to interfere with DNA repair polymerases (e.g., β and γ) as well as lipid biosynthetic enzymes may account for lethal effects in noncycling cells.

Read full chapter

URL: https://www.sciencedirect.com/science/article/pii/B9780323357623000573

Drug-Induced Pulmonary Disease

Megan M. Dulohery MD, ... Andrew H. Limper MD, in Murray and Nadel's Textbook of Respiratory Medicine (Sixth Edition), 2016

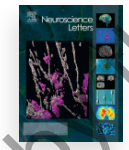
Cytosine Arabinoside

Cytosine arabinoside (ara-C) is a cytotoxic agent used to induce remission in acute leukemia and other hematologic malignancies before bone marrow transplantation. Intensive ara-C treatment regimens have been associated with rapidly fatal noncardiac pulmonary edema (Fig. 71-3).[5] Histologic examination of lung tissue during ara-C pulmonary toxicity reveals substantial accumulation of intra-alveolar proteinaceous material without the cellular atypia and mononuclear infiltration described with other cytotoxic drugs. In two large series, 13% to 28% of the patients with toxicity developed respiratory distress during the administration of the drug, and nearly one half developed symptoms within a month of completing drug administration. The mechanism underlying this reaction is unknown, and the associated mortality is high. Treatment for ara-C pulmonary toxicity is largely supportive, with mechanical ventilation, careful management of fluid status, and surveillance for superimposed infectious complications.

Read full chapter

URL: https://www.sciencedirect.com/science/article/pii/B9781455733835000713

Recommended publications



Neuroscience Letters
Journal

Journal of Neuroscience Methods
Journal

Neuropharmacology
Journal

Neurochemistry International
Journal