Cytosar™ 100 mg - 500 mg, 1 g, 2 g

Cytarabine

Composition

Cytosar™ 100 mg vial + ampoule
I. Cytarabine 100 mg
II. Benzyl Alcohol 45 mg
Water for Injection in a 5 ml ampoule

Cytosar™ 500 mg vial + vial
I. Cytarabine 500 mg
II. Benzyl Alcohol 90 mg
Water for Injection in a 10 ml vial

Cytosar™ 100 mg vial
I. Cytarabine 100 mg

Cytosar™ 1 g vial
I. Cytarabine 1,000 mg

Cytosar™ 2 g vial
I. Cytarabine 2,000 mg

Cytosar™ 1 g and 2 g are primarily intended as single dose packages for high dose therapy. A diluent containing an antibacterial preservative should be used for reconstitution of these products when they will be used for multiple dose administration.

Properties

Pharmacodynamics
Cytosar™ is an anti-metabolite.

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 DNA and RNA has also been reported.

Pharmacokinetics
a) Resorption
Cytarabine is not effective orally; less than 20 percent of the orally administered dose is absorbed from the gastrointestinal tract. Relatively constant plasma levels can be achieved by continuous, intravenous infusion.

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.

There are large variations in plasma cytarabine levels among patients receiving the same dose of the drug. Some studies suggest that the variation is correlated with the clinical response. The chance of obtaining an hematologic remission is good with high plasma levels.

b) Distribution
At plasma levels within the therapeutic range of 0.005 - 1.0 mg/l; 13.3% of cytarabine in plasma was bound to protein. The percentage of bound drug was independent of the drug concentration in the therapeutic range.

After experimental doses of 2 or 3 g/m² cytarabine given intravenously every 12 hours, a high degree of penetration into the central nervous system was demonstrated. Dose levels of this size may permit more complete cytarabine distribution within the dura and piaarachnoid and possibly the brain parenchyma than do standard doses administered intrathecally. In patients given standard doses of cytarabine by continuous subcutaneous and intravenous infusion, CSF level did not vary according to the rate of administration.

c) Biotransformation
Cytarabine is metabolised by deoxycytidine kinase and other nucleotide kinases to the nucleotide triphosphate, an effective inhibitor of DNA polymerase. Cytarabine is converted to its active form by phosphorylation in leukemic blast cells and normal bone marrow. Cytarabine is rapidly deaminated by cytidine deaminase to the inactive metabolite uracil arabinoside (1-ß-D-arabinofuranosyluracil). This process occurs primarily in the liver, but

is present to a lesser extent in blood and other tissues. 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.

d) 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 one to three hours.

With 24 hours about 80% of the administered radioactivity can be recovered in the urine, approximately 90% of which is excreted as 1-ß-D-arabinofuranosyluracil.

Indications

Cytosar™ (cytarabine) is indicated primarily for induction and maintenance of remission in acute non-lymphocytic leukaemia of both adults and children. It has also been found use-ful in the treatment of other leukaemias, such as acute lymphocytic leukaemia, chronic myelocytic leukaemia (blast phase). Cytosar™ may be used alone or in combination with other antineoplastic agents; the best results are often obtained with combination therapy. Remissions induced by Cytosar™ not followed by maintenance treatment have been brief.

Cytosar™ has been used experimentally in a variety of neoplastic diseases. In general, few patients with solid tumors have benefited.

Children with non-Hodgkin's lymphoma have benefited from a combination drug program that includes Cytosar™.

Cytosar™, in high dose 2 - 3 g/m² as an i.v. infusion over one to three hours given every 12 hours for two to six days with or without additional cancer chemotherapeutic agents, has been shown to be effective in the treatment of poor risk leukaemia, refractory leukaemia, and relapsed acute leukaemia.

Cytosar™ alone or in combination with other drugs (methotrexate, hydrocortisone sodium succinate) is used intrathecally for prophylaxis or treatment of meningeal leukaemia.

Dosage and 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 or injection, subcutaneously, or intrathecally.

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

In the induction therapy of acute non-lymphocytic leukaemia, the usual cytarabine dose in combination with other anti-cancer drugs is 100 mg/m² day by continuous i.v. infusion (days one to seven) or 100 mg/m² i.v. every 12 hours (days one to seven).

The literature should be consulted for the current recommendations for use in acute lymphocytic leukaemia.

Intrathecal Use in Meningeal Leukaemia

Cytosar™ has been used intrathecally in acute leukaemia in doses ranging from 5 mg/m² to 75 mg/m² of body surface area. The frequency of administration varied from once a day for four days to once every four days. The most frequently used dose was 30 mg/m² every four 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 leukaemia, as well as in the treatment of meningeal leukaemia.

Sullivan 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/m², hydrocortisone sodium succinate 15 mg/m², and methotrexate 15 mg/m². The physician should be familiar with this report before initiation of the regimen.
Prophylactic triple therapy following the successful treatment of the acute meningeal episode may be useful. The physician should familiarise himself with the current literature before instituting such a program.

Use in children
Cytosar™ use in children is similar to its use in adults.

Reconstitution
Cytosar™ is primarily to be used for preparation of a solution for single dose administration. When used for multiple dose administration, the solvent should contain a preservative.

Cytosar™ sterile powder can be dissolved in water for injection, 0.9% sodium chloride or 5% glucose in water with or without preservative.

For intrathecal administration 0.9% sodium chloride without preservative is recommended.

The maximum concentration that can be obtained after reconstitution with Cytosar™ is 100 mg/ml. In order to have a solution of exact 100 mg/ml the following volume should be added:

ml to add	Cytosar™
4.7 ml	500 mg
9.4 ml	1 g
18.7 ml	2 g

Important

No ampoule file is needed to open the ampoules. The neck of ampoule is prescored at the point of constriction. A colored dot on the ampoule head helps to orientate the ampoule. Take the ampoule and face the colored dot. The ampoule opens easily by placing the thumb on the colored dot and gently pressing downwards.

Contraindications

Cytosar™ (cytarabine) is contraindicated in those patients who are hypersensitive to the drug.

Adverse reactions

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

Following five-day constant infusions or acute injections of 50 mg/m² to 600 mg/m², 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 seven to nine. 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 five days with a peak depression occurring between days 12 to 15. Thereupon, a rapid rise to above baseline occurs in the next 10 days.

Infectious complications
Viral, bacterial, fungal, parasitic, or saprophytic infections, in any location in the body, may be associated with the use of Cytosar™ alone or in combination with other immunosuppressive agents following immunosuppressant doses that affect cellular or humoral immunity. These infections may be mild, but can be severe and at times fatal.

The Cytosar™ Syndrome
A Cytosar™ syndrome has been described. It is characterized by fever, myalgia, bone pain, occasionally chest pain, maculopapular rash, conjunctivitis and malaise. It usually occurs six 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™.

Most frequent adverse reactions

Anorexia, hepatic dysfunction, nausea, fever, vomiting, rash, diarrhoea, thrombophlebitis, oral and anal inflammation or ulceration.

Nausea and vomiting are most frequent following rapid intravenous injection.

Less frequent adverse reactions

Sepsis, pneumonia, cellulitis at injection site, abdominal pain, skin ulceration, freckling, urinary retention, jaundice, renal dysfunction, conjunctivitis, neuritis (may occur with rash), neural toxicity, dizziness, sore throat, alopecia, oesophageal ulceration, anaphylaxis (see Warnings), oesophagitis, allergic oedema, chest pain, pruritus, pericarditis, shortness of breath, headache, urticaria.

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 (2 - 3 g/m^2) schedules of Cytosar™. These reactions include:

- reversible corneal toxicity, and haemorrhagic conjunctivitis, which may be prevented or diminished by prophylaxis with a local corticosteroid eye drop;
- cerebral and cerebellar dysfunction including personality changes, somnolence and coma, usually reversible;
- severe gastrointestinal ulceration, including pneumatosis cystoides intestinalis leading to peritonitis;
- sepsis and liver abscess;
- pulmonary oedema;
- liver damage with increased hyperbiliru-binaemia;
- bowel necrosis;
- neerotizing colitis.

Two patients with adult acute non-lymphocytic leukaemia developed peripheral motor and sensory neuropathies after consolidation with high doses of Cytosar™, daunorubicin and asparaginase. Patients treated with high doses of Cytosar™ should be observed for neuropathy since dose schedule alterations may be needed to avoid irreversible neurologic disorders.

Ten patients treated with experimental intermediate doses of Cytosar™ (1 g/m^2) with and without other chemotherapeutic agents (meta-AMSA, daunorubicin, etoposide) developed a diffuse interstitial pneumonitis without clear cause that may have been related to the Cytosar™.

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.

Cases of cardiomyopathy with subsequent death have been reported following experimental high doses of Cytosar™ and cyclophosphamide therapy when used for bone marrow transplant preparation. This may be schedule dependent.

A syndrome of sudden respiratory distress, rapidly progressing to pulmonary oedema and a radiographically pronounced cardiomegaly, has been reported following experimental high dose Cytosar™ therapy used for the treatment of relapsed leukaemia from one institution. In one case, the outcome of this syndrome was fatal.

Special precautions

Only physicians experienced in cancer chemotherapy should use Cytosar™.

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 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 phys-ician should be familiar with the following text.

Cytosar™ (cytarabine) is a potent bone

marrow suppressant. 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). One case of anaphylaxis that resulted in acute cardiopulmonary arrest and required resuscitation has been reported. This occurred immediately after the intravenous administration of Cytosar™.

If high dose therapy is used, do not use a diluent containing benzyl alcohol. Benzyl alcohol has been reported to be associated with a fatal "Gasping Syndrome" in premature infants. Many clinicians reconstitute with preservative-free 0.9% sodium chloride for injection and use immediately.

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 1,000/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 to 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.

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.

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.

The human liver apparently detoxifies a substantial fraction of an administered dose. In particular, patients with renal or hepatic function impairment may have a higher likelihood of CNS toxicity after high-dose treatment with Cytosar™. Use the drug with caution and possibly at reduced dose in patients whose liver or kidney function is poor.

Periodic checks of bone marrow, liver and kidney functions should be performed in patients receiving Cytosar™.

Like other cytotoxic drugs, Cytosar™ may induce hyperuricaemia 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 measures as might be necessary to control this problem.

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

Two patients with childhood acute myelogenous leukaemia who received intrathecal and intravenous Cytosar™ at conventional doses, in addition to a number of other concomitantly administered drugs, developed delayed progressive ascending paralysis resulting in death in one of the two patients.

Two patients treated with conventional doses of Cytosar™ and daunomycin developed abdominal tenderness (peritonitis) and guaiac positive colitis. Both patients responded to nonoperative medical management. Both patients exhibited neutropenia and thrombocytopenia and were receiving numerous other drugs. The authors recommend careful, conservative management in patients receiving Cytosar™ who appear to have a surgical abdomen, but in whom a definitive surgical diagnosis cannot be made.

Overexposure effects have not been observed in the workplace. Slight eye irritation may be experienced. Repeated or continuous skin contact may cause irritations. In case of accidental contact freely wash the affected area with soap and water.

Intrathecal use

If used intrathecally, do not use a diluent containing benzyl alcohol. Many clinicians reconstitute with preservative-free 0.9% sodium chloride for injection and use immediately.

Cytosar™ given intrathecally may cause systemic toxicity and careful monitoring of the hemopoietic system is indicated. Modification of the anti-leukaemia 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. Necrotising leukoencephalopathy occurred in five 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™. 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.

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

Carcinogenesis, mutagenesis, impairment of fertility

Extensive chromosomal damage, including chromatoid breaks have been produced by cytarabine and malignant transformation of rodent cells in culture has been reported.

Incompatibilities

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

Stability and compatibility after reconstitution

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

Cytarabine is compatible with following drugs, at the specified concentrations, in dextrose 5% in water for eight hours: cytarabine 0.8 mg/ml and sodium cephalothin 1.0 mg/ml; cytarabine 0.4 mg/ml and prednisolone sodium phosphate 0.2 mg/ml; cytarabine 16 mcg/ml and vincristine sulphate 4 mcg/ml.

Pregnancy and lactation

Cytosar™ is known to be teratogenic in some animal species.

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.

Because of the potential for abnormalities

with cytotoxic therapy, particularly during the first trimester, a patient who is or who may become pregnant while on Cytosar™ should be apprised of the potential risk to the foetus 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 all three trimesters of pregnancy, follow-up of such infants would be advisable.

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.

Interactions

Combinations of cytarabine with other antineoplastic or myelosuppressive agents or radiation therapy enhance cytotoxic as well as immunosuppressive activity of drugs in some instances.

A reversible decrease in steady-state plasma digoxin concentrations and renal glycoside excretion followed one cytostatic dose of Cytosar™. Digoxin levels should be closely monitored during cytostatic drug therapy. Steady-state digitoxin plasma concentration did not appear to change. The utilization of digitoxin for such patients may be considered as an alternative.

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.

Clinical evidence in one patient showed possible inhibition of fluorocytosine efficacy during Cytosar™ therapy. This may be due to potential competitive inhibition of its uptake.

Overdosage

There is no antidote for Cytosar™ overdosage. Doses of 4.5 g/m² by i.v. infusion over one hour every 12 hours for 12 doses has caused an unacceptable increase in irreversible CNS toxicity and death.

Storage

Store unreconstituted product at controlled room temperature (15 - 30°C).

Following reconstitution with a diluent containing a preservative, the resulting solution may be stored at controlled room temperature for 48 hours. Following reconstitution with a preservative free diluent, use resulting solution as soon as possible in order to maintain the sterility of the solution.

Shelf-life

60 months.

Pack

Powder for injection
100 mg : for i.v., i.t., and s.c. use.
500 mg, 1 g and 2 g : for i.v. use.

If used intrathecally, do not use a diluent containing benzyl alcohol. For intrathecal administration 0.9% sodium chloride without preservative is recommended.

Powder for injection
Bottle of 100 mg + 5 ml sterile solution and antibacterial preservative.
Bottle of500 mg + 10 ml sterile solution and antibacterial preservative.
Bottle of 100 mg.
Bottle of 1,000 mg.
Bottle of 2,000 mg.