Cytomia

Cytarabine USP 100 mg Injection

COMPOSITION

Cytomia Injection: Each vial contains Cytarabine USP 100 mg (100 mg / 1 ml).

CLINICAL PHARMACOLOGY

Mechanism of Action:

Cytarabine is an antineoplastic agent. Cytarabine is a synthetic pyrimidine nucleoside, which is converted intracellularly to the nucleotide, cytarabine triphosphate. The exact mechanism of action of cytarabine is not fully understood, but cytarabine triphosphate appears to inhibit DNA synthesis by the inhibition of DNA polymerase. Cytarabine's actions are cell-cycle specific. Cytarabine is also immunosuppressant and has demonstrated antiviral activity in vitro.

Pharmacodynamics and Pharmacokinetics:

Cytarabine is not effective when administered orally. It is rapidly and widely distributed into tissues. Cytarabine crosses the blood-brain barrier to a limited extent and also apparently crosses the placenta. After rapid IV injection, plasma concentrations of cytarabine appear to decline in a biphasic manner with an initial distribution half-life of about 10 minutes, followed by an elimination half-life of about 1-3 hours.

Cytarabine is rapidly metabolised, mainly in the liver, to the inactive metabolite 1-β-D-arabinofuranosyluracil. About 70 to 80% of a dose is excreted through urine within 24 hours; approximately 90% as the metabolite and 10% as unchanged cytarabine.

INDICATIONS

Cytarabine may be used alone or in combination with other chemotherapeutic agents. It is indicated for induction of remission of leukaemia, particularly for acute myeloid leukaemia, in adults and children.

Cytarabine has been used for remission induction in acute lymphocytic leukaemia, chronic myeloid leukaemia and erythroleukaemia; and in the treatment and maintenance therapy of meningeal leukaemia and other meningeal neoplasms.

Chiidren with non-Hodgkin's lymphoma have benefitted from a combination drug programme (LSA2L2) that includes cytarabine.

DOSAGE AND ADMINISIRATION

Being orally inactive, cytarabine is administered by a variety of parenteral routes: subcutaneously, intravenously either as a bolus "push" or as a continuous infusion, or intrathecally.

Thrombophlebitis has occurred at the site of drug injection or infusion in some patients. Pain and inflammation at subcutaneous injection sites are rare. Subcutaneous injection sites should be rotated around the areas of body fat: the abdomen, thighs and flank region. The drug is generally well tolerated in most instances.

Higher total doses can be better tolerated when administered by rapid IV injection as compared to slow infusion. Such a phenomenon can be explained by the rapid inactivation of the drug and the brief exposure of susceptible normal neoplastic cells to significant levels after rapid injection.

Normal and neoplastic cells appear to respond in almost parallel manner to these two modes of administration and no distind advantage has been established for either.

Clinical experience to date indicates that success with cytarabine therapy depends more on adeptness in modifying day-to-day dosage to obtain maximum leukaemic cell killed with tolerable toxicity, then on the fundamental treatment protocol selected at the start of therapy.Toxicity necessitating dosage modification almost always occurs.

Dosage of cytarabine must be based on the clinical and haematological response and tolerance of the patient so as to obtain optimum therapeutic results with minimum adverse effects. Even though higher total doses of cytarabine can be given by IV injection compared to continuous IV infusion with similar haematologic toxicity, the most effective dosage schedule and method of administration are yet to be established. Moreover, cytarabine is often used in combination with other cytotoxic drugs, thereby necessitating dose modification of cytarabine and other chemotherapeutic agents, and the method as well as the sequence of administration.

Following is an outline of dosage schedules for cytarabine therapy as reported in the literature.

Dosage Schedules:

Single-Drug Therapy in induction remission in adults with Acute Myelocytic Leukaemia:

Cytarabine 200 milligrams/m^2 daily by continuous IV infusion over 24 hours for 5 days (120 hours) - total dose 1000 milligrams/m^2. The course is repeated approximately every 2 weeks. Modifications based on haematologic response should be made.

Cytarabine combination therapy:

Before a combined chemotherapy protocol is instituted, the clinician should be familiar with current literature, precautions, contraindications, adverse reactions and warnings applicable to all the drugs involved in the protocol.

Cytarabine, Daunorubicin

Cytarabine: 100 milligrams/m^2/day, continuous IV infusion (days 1 to 7)

Daunorubicin: 45 milligrams/m^2/day, IV push (days 1 to 3)

Additional courses (complete or modified) as required at 2 to 4 week intervals if leukaemia is persistent.

Cytarabine, Thioguanine, Daunorubicin

Cytarablne:100 milligrams/ m^2/day, IV infusion over 30 minutes every 12 hours (days 1 to 7)

Thioguanine: 100 milligrams/m^2, orally every 12 hours (days 1 to 7)

Daunorubicin: 60 milligrams/m^2/day, IV infusion (days 5 to 7)

Additional courses (complete or modified) as required at 2 to 4 week intervals if leukaemia is persistent.

Cytarabine, Doxorubicin

Cytarabine: 100 milligrams/m^2/day, continuous IV infusion (days 1 to 10)

Doxorubicin: 30 milligrams/m^2/day, IV infusion over 30 minutes (days 1 to 3)

Additional courses (complete or modified) as required at 2 to 4 week intervals if leukaemia is persistent.

Cytarabine, Doxorubicin, Vincristine, Prednisolone

Cytarabine: 100 milligrams/m^2/day, continuous IV infusion (days 1 to 7)

Doxorubicin: 30 milligrams/m^2/day, IV infusion (days 1 to 3)

Vincristine: 1.5 milligrams/m^2/day, IV infusion (days 1,5)

Prednisolone: 40 milligrams/m^2/day, IV infusion every 12 hours (days 1 to 5)

Additional courses (complete or modified) as required at 2 to 4 week intervals if leukaemia is persistent.

Cytarabine, Daunorubicin, Thioguanine, Prednisolone, Vincristine

Cytarabine: 100 milligrams/m^2/day, IV every 12 hours (days 1 to 7)

Daunorubicin: 70 milligrams/m^2/day, IV infusion (days 1 to 3)

Thioguanine: 100 milligrams/m^2 orally every 12 hours (days 1 to 7)

Prednisone: 40 milligrams/m^2/day, orally (days 1 to 7)

Vincristine: 1 milligram/ m^2/day, IV infusion (days 1,7)

Additional courses (complete or modified) as required at 2 to 4 week intervals, if leukaemia is persistent.

Maintenance of Acute Myelocytic Leukaemia (AML) in adults:

Maintenance programs are generally modifications of induction programs. Similar schedules of drug therapy to those used for induction are normally employed. Most programs have a greater interval between courses of therapy during remission maintenance.

Induction and maintenance of Acute Myelocytic Leukaemia (AML) in children:

Childhood AML has been shown to respond better than adult AML given similar regimens. Where the adult dosage is given in terms of body weight or surface area, the paediatric dosage may be calculated on the same basis, being adjusted on the consideration of such factors as age, body weight or body surface area.

Acute Lymphocytic Leukaemia (ALL):

Dosage schedules used in ALL are normally similar to those used in AML with some modifications.

Intrathecal use in Meningeal Leukaemia:

Cytarabine has been used intrathecally in acute leukaemia in doses ranging from 5 mg/m^2 to 75 mg/m^2 of body surface area. The frequency of administration varied from once a day for 4 days to once every 4 days. The most frequently used dose was 30 mg/m^2 every 4 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.

Dosage modification:

Suspension or modification of cytarabine therapy should be considered at the appearance of signs of serious haematologic depression, for example, if the polymorphonuclear granulocyte count falls below 1000/mm^3 or the platelet count falls below 50,000/mm^3. Such guidelines may be modified, depending on signs of toxicity in other systems and on the speed of fall in levels of formed blood elements. Therapy should be recommended when definite signs of bone marrow recovery appear and the above granulocyte and platelet levels are attained. If therapy is withheld until peripheral counts of blood elements return to normal, cytarabine may be ineffective.

Cytarabine Injection is a ready to use solution with a concentration of 100 milligrams per ml. It is suitable for intravenous use and in small volumes may also be used subcutaneously. Cytarabine Injection 100 milligrams per ml is hypertonic and therefore unsuitable for intrathecal use unless diluted appropriately.

Cytarabine is a potent bone marrow suppressant. Patients receiving the drug must be kept under close medical supervision. Leucocyte and platelet counts should be performed daily and frequent bone marrow examinations conducted. Facilities should be available for management of complications of bone marrow suppression.

Two patients with childhood acute myelogenous leukaemia who received intrathecal and intravenous cytarabine 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.

Cytarabine should only be used under constant supervision by physicians experienced in therapy with cytotoxic agents.

Hyperuricaemia secondary to rapid lysis of neoplastic cells may occur in patients receiving cytarabine; serum uric acid concentrations should be monitored.

Periodic determinations of renal and hepatic function should also be performed.

The drug should be used with caution and at reduced doses in patients whose liver function is poor as the liver apparently detoxifies a substantial fraction of an administered dose.

Acute pancreatitis has been reported to occur in patients being treated with cytarabine who have had prior treatment with L-asparaginase.

Patients treated with high dose cytarabine should be observed for neuropathy since dose schedule alteration may be needed to avoid irreversible neurological disorders.

Use in Children:

Appropriate studies with cytarabine have not been performed in the paediatric population. However, paediatric specific problems that would limit the usefulness of this medication in children are not expected.

Use in the Elderly:

Although studies with cytarabine have not been performed in the geriatric population, geriatric specific problems that would limit the usefulness of this medication in the elderly are not expected. Elderly patients are, however, more likely to have age related renal function impairment, which may require reduction of dosage in patients receiving cytarabine.

Mutagenicity:

Cytarabine may cause chromosomal damage, including chromatoid breaks, in humans. Malignant transformation of rodent cells in culture has been reported.

Carcinogenicity:

Secondary malignancies are potential delayed effects of many antineoplastic agents, although it is not clear whether the effect is related to their mutagenic or immunosuppressive action. The effect of dose and duration of therapy is also unknown, although risk seems to increase with long-term use.

Use in Pregnancy:

Cytarabine is suspected to have caused or may be expected to cause an increased incidence of human fetal malformations or irreversible damages. It may also have adverse pharmacological effects. Cytarabine has been shown to be teratogenic in some animal species and should not be used during pregnancy, especially during the first trimester, not in women likely to become pregnant.

Use in Lactation:

It is not known whether cytarabine is excreted in human milk. Women should be advised not to breast feed while being treated with cytarabine, because of the risks to the infant.

Effects on ability to drive and use machines:

Cytarabine for Injection is likely to produce severe adverse effects, which may impair the patient's ability to concentrate and react and therefore constitute a risk in the ability to drive and use machines.

CONTRAINOICATIONS

Cytarabine is contraindicated in patients with known hypersensitivity to the drug.

OVERDOSE

Severe bone marrow depression, gastrointestinal toxicity and vomiting are among the signs and symptoms expected. Treatment with cytarabine should be ceased and supportive measures instituted. In bone marrow depression, transfusions of blood products may be required and active measures may be necessary to combat infection.

Hyperuricaemia is avoided by the addition of allopurinol to treatment schedules and measures such as alkalinisation of . the urine and hydration may also be adopted.

Techniques attempting to prevent the occurrence of alopecia have met with varying success. Scalp tourniquets and ice packs have been used to minimize concentrations of antineoplastic agents in the scalp after intravenous injection. Such methods, however, may allow the development of a cancer-cell sanctuary and should not be used in patients with leukaemia or other conditions with circulating malignant cells.

The treatment of extravasation is controversial. Warm moist soaks or ice packs have been applied and a corticosteroid may sometimes be instilled into the affected area.

Antiemetic therapy should be given in an attempt to prevent or control nausea and vomiting.

ADVERSE EFFECTS

The major adverse effect of cytarabine is haematologic toxicity. Myelosuppression is normally manifested by megaloblastosis, leucopenia, anaemia, reticulocytopenia and thrombocytopenia. Leucopenia follows mainly from granulocyte depression; lymphocytes are minimally affected. The severity of these adverse effects is dependent on the dose of the drug and schedule of administration.

Incidence and severity of haematologic toxicity is minimal after a single intravenous dose of cytarabine, but myelosuppression occurs in almost all patients with daily IV injections or continuous IV infusions of the drug.

Nausea and vomiting may occur in patients on cytarabine therapy, and usually occur more frequently and severely following rapid IV administration as opposed to continuous infusion of the drug.

Viral, bacterial, fungal parasitic or saprophytic infection which can be mild, severe and at times fatal, may be associated with the use of cytarabine when used alone or in combination with other immunosuppressive agents following immunosuppressive doses that affect cellular or humoral immunity.

Neurotoxicity following intrathecal cytarabine has been associated with preservative containing diluents and many clinicians recommend the use of preservative free diluents instead.

A cytarabine syndrome characterised by fever, myalgia, bone pain, malaise, maculopapular rash, conjunctivitis, and occasionally chest pain, has been reported. A "flu-like" syndrome has been reported, which may be treated with corticosteroid therapy if severe. Anaphylactoid reactions have occurred.

It normally occurs at 6 to 12 hours after administration of the drug; corticosteroids have been shown to be of benefit in the treatment and prevention of the syndrome. If treatment of the symptoms of the syndrome is required, administration of corticosteroids should be considered, as well as continuation of cytarabine therapy.

Two patients with adult non lymphocytic leukaemia developed peripheral motor and sensory neuropathies after consolidation with high dose cytarabine, daunorubicin and asparaginase.

A syndrome of sudden respiratory distress, rapidly progressing to pulmonary oedema and radiologically pronounced cardiomegaly has been reported following experimental high dose therapy of cytarabine for relapsed leukaemia. This syndrome can have fatal consequences.

PHARMACEUTICAL INFORMATION

Storage Condition:

Store the vial in original carton at 15°C to 30°C. Protect from light. Do not refrigerate. Keep out of the reach of children.

Presentation & Packaging:

Cytomia Injection: Each commercial box contains 1 vial of Cytarabine 100 mg Injection.

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UNIT-2
Tongi, Gazipur