Fluroxan

Fluorouracil

Solution for IV Injection or Infusion

COMPOSITION:

Fluroxan 250 Injection :
Each vial contains 10 ml of solution containing Fluorouracil BP (5-fluorouracil) 250 mg as 25 mg / ml.

Fluroxan 500 Injection :
Each vial contains 10 ml of solution containing Fluorouracil BP (5-fluorouracil) 500 mg as 50 mg / ml.

PHARMACOLOGICAL INFORMATION:

Mechanism of Action

Fluorouracil is inactive as such in mammalian cells but is converted into the active 5-fluorodeoxyuridine monophosphate (FdUMP) by a variety of different metabolic pathways. The drug works by inhibiting the enzyme thymidylate kinase which results in reduced formation of thymidine and thus of DNA. The active metabolite FdUMP appears to form a stable complex with the folate cofactor N-5, 10-methylene tetrahydrofolate which inactivates thymidylate kinase. Fluorouracil as FdUMP is also incorporated into RNA which results in fluorination of RNA. The effect of fluorouracil on living cells is limited mainly to those in the proliferative phase but while cells in the G2 and S phase are most affected there may be effects at any stage of the cell cycle.

Pharmacokinetics

5-fluorouracil is rapidly metabolized in the liver to produce biologically inactive metabolites which are eventually converted to carbon dioxide, eliminated by the lungs. 80% of 5-fluorouracil can be accounted for by conversion to respiratory carbon dioxide within 12 h of administration. 15% of the drug is excreted through urine.

CLINICAL INFORMATION:

Therapeutic Indications

Fluorouracil is indicated alone or in combination for-

1. Carcinoma of the colon or rectum
2. Carcinoma of the stomach and exocrine pancreas
3. Carcinoma of the liver
4. Carcinoma of the breast
5. Carcinoma of the bladder
6. Carcinoma of the lung
7. Epithelial ovarian carcinoma
8. Cervical carcinoma

Dosage and Administration

Intravenous 5-fluorouracil can be delivered by rapid intravenous bolus injection or slow infusion.

The vial contents can rapidly be injected directly into a peripheral vein, the commonest schedules being:

12-13.5 mg/Kg (500 mg/m^2) daily for 5 days repeated at

4-weekly intervals.

Slow intravenous infusion requires the drug, to be diluted in 500 ml of dextrose 5% solution, then infused over 2-3 h on 5 successive days.

Usual Adult Dose:

For palliative management of cancer:

Initial Dose: 12 mg/kg intravenously once daily for 4 successive days.

Maximum Dose: 800 mg/day.

If no toxicity is observed, 6 mg/kg may be administered on the 6th, 8th, 10th, and 12th day (No therapy is given on days 5, 7, 9, or 11). Discontinue at the end of day 12, even with no apparent toxicity.

Poor risk patients and those who are not in an adequate nutritional state:

Initial Dose: 6 mg/kg/day for 3 days.

Maximum Dose: 400 mg/day.

If no toxicity is observed, 3 mg/kg may be administered on days 5, 7, and 9 (No therapy is to be administered on days 4, 6, or 8). Discontinue at the end of day 9, even with no apparent toxicity.

Maintenance Therapy:

In instances where toxicity has not been a problem, it is recommended that therapy be continued using either of the following schedules:

1) Repeat the dosage of the first course every 30 days after the last day of the previous course, or

2) When the toxic signs resulting from the initial course of therapy have subsided, administer a maintenance dose of 10 to 15 mg/kg/week as a single dose.

Maximum Dose: 1g/week The reaction by the patient to the previous course of therapy should be taken into account and the dosage should be adjusted accordingly.

Usual Adult Dose for Cervical Cancer:

In combination with cisplatin 1gm/m^2 IV on day 1. The cycle is repeated every 21 days.

Usual Pediatric Dose for Malignant Disease:

The manufacturer has reported that the safety and effectiveness of fluorouracil have not been established in children. However, the drug has been used in children following adult guidelines.

Intra-arterial Infusion:

Fluorouracil has also been given by intra-arterial infusion for adult in doses of 5 to 7.5 mg/kg body weight is dissolved in 20-100 ml of 5% Dextrose solution and administered 10-20 days by using an infusion pump.

Combination with Radiation:

Usual adult daily dose of 5-l0 mg/kg body weight is given in combination with radiation according to systemic administration method or intra-arterial infusion method.

Combination with Other Anticancer Drugs:

Fluorouracil is used alone or in combination in the adjuvant treatment of breast and gastro-intestinal cancer, and palliation of inoperable malignant neoplasms, especially those of the gastro-intestinal tract, breast, head and neck, liver, genito-urinary system, and pancreas. It is also used with cyclophosphamide and methotrexate in the combination chemotherapy of breast cancer.

An usual adult dose of 5 to l0 mg/kg body weight daily is given in combination with other anticancer drugs everyday or intermittently once to twice a week by systemic administration method or intra-arterial infusion method.

Side Effects

Potentially life-threatening effects

Severe effects from 5-fluorouracil are related to the dosage and duration of therapy.

Cardiac effects:

Occasional case reports associating 5-fluorouracil therapy with 'ischemic cardiac events' evidence against the autoimmune phenomenon is the fact that in several cases cardiotoxicity occurred within several hours of the first dose.

Hematological effects:

Potentially lethal effects caused by severe hematological toxicity may develop within the first 10 days of treatment being instituted but generally resolves within 3 weeks. At the recommended dose and schedule it is rather uncommon for hematological toxicity to be severe. Any agent which causes suppression of the bone marrow will contribute to severe effects from 5-fluorouracil on the blood-forming cells. Thus extensive prior irradiation or the concomitant use of cytotoxic drugs tend to exacerbate the severity of the hematological side effects of 5-fluorouracil.

Neurological effects:

Effects on the central nervous system have been occasionally reported and cerebral ataxia is dose-dependent with an incidence of between 3.1 and 7%. Acute cerebellar syndromes and myelopathy have been described following intrathecal 5-fluorouracil. Neurological syndromes may occur rarely after carotid artery perfusion in head and neck cancer.

Other effects:

Allergic reaction (including difficulty in breathing, closing of the throat, swelling of the lips, tongue, or face, or hives), decreased bone marrow function and blood problems (extreme fatigue, easy bruising or bleeding, black, bloody or tarry stools, or fever, chills, or signs of infection), hand-foot syndrome (tingling, pain, redness, swelling or tenderness of the hands and feet), severe vomiting, diarrhoea, frequent bowel movements or watery stools, or sores in the mouth or throat, or stomach pain or heartburn or black, bloody or tarry stools. Other less serious side effects may include mild to moderate nausea, vomiting or loss of appetite, balance problems, confusion, rash and itching, or temporary hair loss.

Conjunctivitis, both acute and chronic can proceed to tear duct stenosis and ectropion following prolonged administration. Very chronic administration, extending beyond 3 months, of low dosage has been associated with low systemic toxicity but includes the possibility of painful and tender hands and feet associated with erythema of the extremities.

Contraindications

Pregnancy:

Fluorouracil is contraindicated throughout pregnancy. The literature pertaining to pregnancy and cytotoxic drugs is necessarily limited but it appears in general that risk of teratogenesis diminishes with the advancement of pregnancy. Therefore most cytotoxic drugs are absolutely contraindicated in the first trimester and 5-fluorouracil, used in the first trimester has been reported to cause multiple congenital abnormalities. There are many case reports, however, of pregnancy being conducted successfully with combination chemotherapy being given to the mother during the second and third trimesters. Because of the age of the population and the natural history of the tumors treated, most of the data on long-term follow-up pertain to therapy for leukemias. More data need to be accrued on the subsequent development of neonates before it is certain that any of these compounds are free of late effects.

Precaution and warning

5-fluorouracil is highly toxic drug with a narrow margin of safety. Therefore patients should be carefully supervised, since therapeutic response is unlikely to occur without some evidence of toxicity. Daily dose should not exceed 1 gram. Treatment should be discontinued promptly when one of the following signs of toxicity appears:
Leucopenia (WBC under 3500/mm^3). Thrombocytopenia (platelet under 100000/mm^3). Stomatitis (the first small ulceration at the inner margin of the lips is a signal for stopping treatment). Severe diarrhoea (frequent bowel movements and watery stools). Gastro-intestinal ulceration and bleeding.

Drug interaction

Pre-treatment with cimetidine for 4 weeks led to increased plasma concentrations of fluorouracil following intravenous and oral administration in 6 patients. The effect was probably due to a combination of hepatic enzyme inhibition and reduced hepatic blood flow.

Acute overdosage

Cases of deliberate overdose are unknown but excessive duration or dosage of therapy will produce life-threatening toxicity because of the hematological effects as described above. There is no specific antidote to 5-fluorouracil toxicity; treatment consists in supportive care. In addition to the hematological toxicity other toxicities will occur with overdose.

High risk groups

Neonates:

No dosage recommendations are made for neonates.

Lactating mother:

It is not known whether fluorouracil is excreted in human milk. Because fluorouracil inhibits DNA, RNA and protein synthesis, mothers should not nurse while receiving this drug.

Children:

Safety and effectiveness in children have not been established.

The elderly:

No special precautions are required, doses being adjusted for the patient's weight and height.

Symptoms and treatment for overdose and antidote

Sign and symptoms are qualitatively similar to the side effects. Treatment should be performed promptly and appropriate drugs are given to control symptoms of overdose.

Instructions for Use, Handling and Disposal

5-Fluorouracil is a cytotoxic anticancer drug and, caution should be exercised in handling 5-Fluorouracil. Special, trained personnel should reconstitute the drug. Preparation requires a room reserved for this purpose. The work surface should be covered with disposable plastic-backed absorbent paper. Smoking, eating and drinking are prohibited in the room. The handling staff must have a set of appropriate equipment, particularly long-sleeved coats, protective masks, caps, protective goggles, sterile disposable gloves, worktop protection sheets and waste collection containers and bags. If 5-Fluorouracil solution contacts the skin, wash the skin immediately and thoroughly with soap and water. Following topical exposure, events have included tingling, burning and redness. If 5-Fluorouracil contacts mucous membranes, the membranes should be flashed thoroughly with water. Pregnant women must be warned and avoid handling cytotoxic agents. All broken containers must be treated with the same precautions and regarded as contaminated waste. Contaminated waste is to be disposed of by incineration in rigid containers labeled for this purpose or must be destroyed as per the government rules.

PHARMACEUTICAL INFORMATION:

Storage conditions

Store the vial in original carton below 25^{0}C (do not refrigerate). Protect from light. Keep out of the reach of children.

Presentation

Fluroxan 250 Injection :
Each box contains one vial of 10 ml solution.

Fluroxan 500 Injection:
Each box contains one vial of 10 ml solution.

LF01602

Manufactured By
BEACON
Pharmaceuticals Limited
Mymensingh, Bangladesh