Translation

Ministry of Public Health of Ukraine
Pharmacological Committee

"This instruction is certified"
The chief of Pharmacological Committee

29.12 1998

INSTRUCTION
on clinical study of preparation AMITOZYN

Amitozyn is an original antitumour preparation from a new group of antiblastoma substances: alkaloids of Chelidonium Majus L. modified with ThioTEPA.

Composition per 1ml : amitozyn / 0.01, 0.25 g /
solvent / 1 ml /

Refined from impurities the preparation is brown small-crystalline substance. Its solution is prepared using a special procedure. Under ultraviolet rays with 3000 Angstrom wavelength the amitozyn fluoresces giving the light of yellow-orange colour. The concentrated solution of the amitozyn is stable but can be decomposed on long exposing to light and boiling.

The pharmacological characteristics. The amitozyn is a product of alkylation of celandine alkaloids with ThioTEPA. The preparation has cytostatic (antitumour) and immunomodulating action and initiates resolution of tumours of mammals with MTCh sarcoma, Gerer carcinoma , lympoid leucosis LIO-1, Erlih carcinoma of mice (hypodermic variant), Kroker sarcoma of mice, Broun-Pirs carcinoma of rabbits (intramuscular inoculation), Plis lymphosarcoma , hepatoma RS-1, Uoker carcinosarcoma , Garding-Passi melanoma , HOP carcinoma of hamsters.

In contradiction to the most part of existing now antitumour preparations the amitozyn does not inhibit leukopoiesis and has an insignificant toxicity. Therefore, it can be applied both to combined treatment and to the irradiation.

Amitozyn induces differentiation and apoptosis of tumour cells and their death owing to mitosis arrest and disturbance of synthesis of DNA, RNA, oxidation-reduction processes.

Pharmacokinetics. In all the ways of injection the amitozyn is revealed in tumour tissue by the luminescence method owing to yellow fluorescence some minutes later. Active ethylenemine groups are determined by biochemical way mainly in tumour after several hours and are upkept here in the therapeutical concentration during 48-120 hours. The lesser part of the preparation is contained in other tissues and internal organs. Penetrating into tumour cells, it combines with DNA, provokes of disturbing its synthesis and degradation of molecule.

Indications for testing and application.

1. Epythelium malignant tumours of mamma, thyroid glands, ovary, neck of uterus, urinary, prostate, larynx, esophagus, cardial section of stomach, tongue, liver, intestine.
2. Connective malignant tumour of uterus, prostate.
3. Melanoblastoma.
4. Non-malignant tumours of derma, polyps of nose, larynx, stomach, urinary, urethra, rectum, fibromyoma of uterus, mastopathy.
5. The preparation can be applyed also for treatment other tumours and systemic diseases: lymphogranulomatosis, acute misloid leucosis after non-effected using the traditional methods of treatment.
6. Systemic, immune and immuno-viral diseases: non-specific polyarthritis, lupus erythematosus, meningoencephalitis.
7. The preparation is useful to apply when big growing of connective tissue is observed and for treatment of hyperkeratosis.

Owing to absence of leucopoiesis inhibition the amitozyn can be applied at once after irradiation and treatment with other antitumour preparations. Taking into account of the results of the preliminary clinical investigations which were carried out at some scientific and production institutes of Ukraine it is expedient to apply the amitozyn together with the irradiation treatment.

Techniques for use and doses. The amitozyn can be injected by intravenous, intramuscular, intrapleural, intraperitoneum, rectal ways and can be applied for external use. When no remote metastases exist, the preparation can be injected directly into a tumour.

The most convenient procedures are intravenous, intramuscular, and rectal injections. For these purposes the ready standard solution of the preparation is injected immediately by intramuscular way or before injection the amitozyn is solved in 5ml of isotonic solution (0.85%) of sodium chloride (NaCl), intermixed intensively and injected by intramuscular way in upper-outer square of seat by the needle of the medium size. The prepared homogeneous dark-brown solution must be injected during 3 – 5 minutes. In the same doses the amitozyn can be introduced into a rectum with the help of a micro–clister. For the intravenous, intrapleural, intraperitoneal injections the amitozyn is solved in 5 – 10 ml of isotonic solution of sodium chloride and is injected slowly by flow , or it is solved in the volume of 100 – 200 ml and Introduced by drop.

At specialized clinics the amitozyn can be used in the regional chemotherapy.

For the first five injections the preparation dose is 0.25 mg/kg on an injection. If the preparation is well endured, the dose is increased to 0.5 mg/kg and then in the absence of side effects, after 10 injections the dose is increased to 0.75 mg/kg.

Intervals between injections must be 48-120 hours. Duration of treatment (15-20 injections) amounts 1 - 1.5 month. Number of the injections is dependent on a rate of resolution of tumour and its sizes, but is not less than 10 - 15 injections.

According to the method of tumour treatment and because of a possibility of non-total resolution of a tumour during a first course, after a month interval or, if the preparation is endured well, after 10-20 days the analogous second course is carried out. After 3 month interval, two courses with 10 injections are performed using 6 month break between them.

In the first two years after clinical resolution of tumour it is necessary to make the profilaxis courses including 10 injections every 6 months and in the next 5 years to perform one course in a year.

Concentrated solution of the amitozyn can be used locally and as micro-clister into rectum with the same intervals and doses, especially for tumours of a small pelvis and for children.

Side-effects, Possible side symptoms, their prevention and methods of struggle :

a) in case of intramuscular way of injection near a seat nerve, stretching pains along the nerve are possible, therefore, an injection must be performed only in an upper-outer square of a seat;

b)infiltrates after injection under derma and to the place of a previous injection;

c)shooting pain in the site of the main tumour and metastases, that can be occured usually on the first or second day after preparation injection, is stopping without treatment;

d)after the amitozyn injection into tumour directly, the latter can be enlarged on account of edema which is kept during a few days;

e)a slight rising of temperature (from o,5 to 2^0C) within 8 – 10 hours after intramuscular injection and within 1 – 4 hours after intravenous one.

When a tumour is resolving intensively it is necessary to decrease the intoxication with the help of such actions : transfusion of plasma, saline solution, blood, and using vitamins, especially B_6 and C at one-time dose 5mg/kg, complex of medicinal plants (Echinacea., Eleutherococcus, Polemonium coeruleum).

Contra-indications. Individual intolerance of the preparation, serious affection of cor with symptoms of cardiovascular incompetence, toxic hepatitis, kidney affection with symptoms of kidney incompetence, terminal phases of disease.

The form of output. The specially stabilized water solution of the preparation is produced in sterile bottles on 5 or 10 ml with concentrations 10 and 25 mg/ml.

The conditions of storage. Group B. The preparation must be held hermetically sealed in the bottles (it is better from dark glass) and kept in a dark cool place at the temperature from 0 to 10^0C. The optimum temperature is $+4^0$C. The term of storage is 5 years.