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COMPARISON OF THE EFFECT OF COLCHIPRIT-NEO WITH KNOWN CYTOSTATICS AND STUDY OF ITS EFFECT ON IMMUNITY

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Abstract: The oral toxicity of colchipritol was 33-97 times lower than that of parenteral colchipritol, as well as its higher activity on used tumor strains, which was close to 90% and higher than that of reference drugs. Colchiprite- neo, when administered orally, is a substance capable, along with high antitumor activity, of stimulating immunity at a therapeutic dose, which is explained by its ability to stimulate CFUs.

Key words: new drug colchiprit-neo, activity, immunomodulatory effect, influence on CFUs.

As you know, one of the most popular treatment methods - chemotherapy, as a rule, gives pronounced general toxic effects, rapidly developing resistance, has a noticeable immunosuppressive effect, which dictates the need to create new more effective anticancer drugs, with greater selectivity and reduced side effects. This study investigated the activity of a new formulation of colchiprite- neo colchiprit- derivative (the so-called oral K-20) and compared it with known cytostatics to identify advantages over existing drugs. It was also interesting to study the effect of this drug on immunity, since an example of substances that stimulate the immune system after treatment at high therapeutic doses was the new chloroethylamine derivatives of colchicine: K-42 and K-48 obtained in the MSCID of the Ministry of Health of the Republic of Uzbekistan [1,2].

The aim of the work was to study the activity of a new drug in animals with tumor strains in comparison with known cytostatics and to study its effect on immunity

Materials and methods. The subject of the study was a colchiprita-neo drug synthesized from colchicine in the MRMSC of the Ministry of Health of the Republic of Uzbekistan. The specific (antitumor) activity of colchiprit-neo was studied by daily oral administration to animals (mice and rats) with recurrent tumors for 10 and 8 days at single doses of 100 mg/kg in mice, and at a dose of 30 mg/kg in rats. Experiments were carried out both in the early and late period after the transplantation of tumors with a different number of injections. Tumors were transplanted according to conventional methods: tumors were grafted subcutaneously with a suspension of tumor cells 30-60 mg in 0.3-0.5 ml of culture medium per mouse [3]. Treatment of the animals was initiated 3-4 (or 10 and 15) days after tumor implantation. The new drug was administered intraperitoneally and orally daily 1 times a day for 10 days at doses of 100 mg/kg to mice and 30 mg/kg to rats; comparators were administered at TD doses. Control animals received adequate vehicle on the days of dosing. Not earlier than 7 days after the last administration of the drug, animals were sacrificed using humane methods of working with laboratory animals. Before administration and at the end of the experiment, the body weight of the animals was determined. To study tumor growth dynamics in mice and rats of treated and control groups, tumor volume was measured in 3 projections at the beginning of the experiment and then every 5 days until sacrifice. Tumor growth inhibition was calculated from formulas [3]

by volume (V) and weight (M) of the recovered tumor. The tolerability of treatment was judged by the death of mice, to indirectly assess possible hematotoxicity in dead and euthanized mice, spleen weight and some hematological parameters were determined.

The immune status parameters were studied in vivo - in the circulating blood of animals on the day of slaughter according to the guidelines of the Institute of Immunology of the Russian Federation and the Institute of Immunology of the Academy of Sciences of the Republic of Uzbekistan, and the immunological effect of the new compound was studied by determining the number of antibody-forming cells (AOC) in the spleen using the method of local hemolysis of erythrocytes according to Erne and Nordin in the modification of Lefkovits I., (1981).

To study the effect of the compounds on the number of endogenous colony-forming units in the spleen (CFUs), mice were irradiated on a Theratron-780-Ye apparatus at a sublethal dose of 6 Gy, two hours after irradiation, preparations were administered once at different (therapeutic and 1 mg/kg) doses. On the 9th day, the animals were killed under ether anesthesia and the change in body weight, spleen, as well as the number of endogenous colony-forming units in the spleen were taken into account according to the method of TillJ.E., McCulloch E.A. [4]. After the spleens were removed and the colonies were counted, they were fixed in Buena fluid, after which the microcolonies were counted. Statistical processing was performed using Statistica version 6.0. $P < 0.05$ was taken as the level of statistical significance

Results obtained. So, on 4 tumor strains (ESR, Sarcoma 180, KSU and Sarcoma 45), the antitumor effect of colchipritol-neo is higher than the effect of xeloda, taxol, etoposide, cisplatin, doxorubicin, 5-fluorouracil and cyclophosphane (Table 1), it should also be noted that the effect of colchipritol It was not accompanied by side effects, as in comparators, such as death of animals, decrease in body weight, spleen and hematopoietic parameters.

Table 1. Comparison of colchiprit-neo action with known cytostatics

route of administration, dose	solid tumor ERLICHA (SOE)	Sarcoma 180	Carcinosarcoma Walker (KSU)	Sarcoma 45
	tumor growth inhibition (TPO)% (v/w)			
Colchiprit intraperitoneal - 4mg/kg-mice, 2-rats	82/86	41/45	59/56	70/70
Colchiprit- neo Per"os-100 mg/kg-mice, 60-rats	96/94	92/90	90/90	90/91
Xeloda Per"os 1200 mg/kg-mice, 1000-rats		65/62		61/62
Doxirubicin intraperitoneal -1.5 mg/kg-mice, 0.7-rats		88/90	89/89	82/83
Cisplatin intraperitoneal -6 mg/kg-mice, 4-rats		82/86		83/83
Taxol intraperitoneal -12 mg/kg to mice, 4 rats	88/81	88/90	88/90	83/83
Etoposide intraperitoneal 15 mg/kg-mice, 7-rats	84/84		82/84	84/82
5-Fluorouracil intraperitoneal 15m/kg-mice, 9mg/kg-rats			71/74	61/56
Cyclophosphan intraperitoneal 10 mg/kg in mice and rats	70/73			71/72

A study of chronic toxicity in rats under the influence of the drug colchiprit-neo, administered orally daily for 30 days, showed that the body's response to long-term use of the drug is clearly dose-dependent. The drug in a therapeutic dose with prolonged oral use is well tolerated by animals of both sexes and does not have a pronounced toxic effect on the functions of vital organs and systems. A double dose and a dose increased by 4 times causes a number of negative effects on the kidneys and liver. Effects on other organs are less toxic [6]. All the above data allow us to conclude that the drug does not have a toxic effect on the animal body.

The study of the effect of colchipritol-neo on the immune status parameters was carried out in mice that were digested with S-180 tumor after 8 injections of the drug on the day of slaughter in accordance with the guidelines of the Institute of Immunology of the Russian Federation and the Institute of Immunology of the Academy of Sciences of the Republic of Uzbekistan. Colchiprit-neo administered orally at a dose of 100 mg/kg increases the amount of AOC in tumor carriers compared to the control group (14,000 control, colchiprit-neo- 17,000 AOC per spleen) with a simultaneous increase in spleen weight. Colchipritol at a dose of 4 mg/kg almost halved, reduced AOC compared to the control (8.300 -K-20). Studies of surface receptors of lymphocytes carried out in the productive phase of the immune response after administration of the drug showed that Colchirite -neo caused stimulation of all studied surface receptors from 1.1 to 1.56 times**.** Thus, two methods showed that colchiprit-neo stimulates immunity both by determining the number of antibody-forming cells (AOCs) and by using monoclonal antibodies

It should be noted that colchiprit-neo, due to its structural features, due to the introduction of a dichloroethylamine fragm A study of the effect of colchipritol-neo on CFUs revealed its active effect on hematopoietic function through the ability to stimulate CFUs. Colchipritol at oral doses of 1 and 100 mg/kg after radiation exposure contributes to an increase in the number of micro- and macrocolonies (CFUs) to 9.5 + 3.4 and 22.0 + 3.4, respectively, as well as an increase in the weight of the spleen and thymus compared to the irradiated group. This was reflected in its immune status when TD was administered, since it is one of the factors that stimulate the formation of new hematopoietic and immunocompetent cells and thereby seem to contribute to the restoration of peripheral blood counts. Colchicine in the literature [V.V. Kholin, 1979] is classified as radiomimetics, substances similar in effect to radiation, therefore, their ability to induce CFUs is understandable. ent into the colchicine molecule, which converts it into a substance of a freely radical nature [2], is also a radiomimetic and thereby contribute to more significant stimulation of CFUs.

Conclusions

1. In all tumor strains used, Colchiprit-neo activity was higher than in parenteral use and was higher than the activity of comparators with or without side effects

2. Colchipritol-neo, when administered orally, is a substance capable, along with high antitumor activity, of stimulating immunity at a therapeutic dose, which is explained by the ability to stimulate CFUs.

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