disease leads worth outcomes, requires surgical interventions and causes increasing frequency of complications Therefore, early diagnosis is the most important factor related to outcome. Screening for DDH is essential in all newborns, physical examinations revealing alterations must be complemented with ultrasound imaging study to avoid the delayed diagnosis of the condition and therefore decrease incidence of the complications.

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STUDYING THE POSSIBILITY OF REDUCING TOXIC EFFECTS OF CHEMOTHERAPY USING THE NEW DERIVATIVE KOLCHAMIN K-48 ON STRAIN OF SARCOMA - 180

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SUMMARY

Studies on an experimental tumor strain of sarcoma-180 in BALB / c mice showed that the combined use of cisplatin and vincristine with a new derivative of colchamine K-48 increases their own antitumor activity, while reducing the toxic effects of the treatment. In addition, this combined use of well-known cytostatics with a new drug made it possible to eliminate the death of experimental animals caused by their toxic effects and reduce such side effects as weight loss and spleen, as well as increase the level of leukocytes.

Key words: antitumor activity, chemotherapy toxicity, colchamine derivative, hematopoietic stem cells, sarcoma- 180.

At present, an important aspect of the study of potential antitumor drugs is the study of various aspects of their biological action, which allows us to predict to a certain extent the area of their specific application in clinical practice, where the main requirements are the possibility of their long-term use and the absence of toxic manifestations that would exceed the effectiveness of growth inhibitory actions. With malignant growth, an imbalance develops between the intensity of production of antioxidant enzymes and free radical oxidation, as well as the level of functional activity of the antioxidant defense system. The use of chemotherapy in the treatment of malignant tumors inevitably leads to an increase in metabolic changes in the body and the development of various toxic complications [3,6,7].

A number of derivatives of colchicine and colchamine, created in the laboratory of antitumor drugs *Republican Specialized Scientific and Practical Medical Center of Oncology and Radiology of the Ministry of Health of the Republic of Uzbekistan* and having low toxicity and high antitumor effects, were found to stimulate the formation of colony forming units in the spleen (CFU) in experimental mice, in particular, the drug K-48, which more pronounced when applied in small doses (1 mg / kg). Apparently, this compound is an inducer of colony stimulating factor at one of the stages of differentiation of hematopoietic stem cells [1,3,4].

A study of the effect of cytostatics on the number of CFUs provides an idea of the extent to which a particular compound causes a change in the proliferative activity of a population of hematopoietic stem cells, which is empty by radiation, which enhances the ability to predict its therapeutic effect. Each colony of CFUs in the spleen of sublethally irradiated mice consists of ~ 106 immature cells of an erythroid, myeloid, or megakaryocyte germ, which are the offspring of one cell, which, together with the ability of these cells to self-maintain, allows them to be considered stem hematopoietic cells [3,5].

It turned out that the higher the level of CFU in animals when exposed to derivatives of colchicine and colchamine, the more noticeable will be their specific ability to exert a stimulating effect on the immune system and hematopoiesis. Moreover, when the aforementioned drugs are used in therapeutic antitumor doses, their toxic effects do not appear or are weaker than those of other cytostatics, apparently due to the ability to stimulate certain hematopoiesis units [2,5,19-20]. It was previously shown that K-48 at a therapeutic dose of 100 mg / kg on 7 strains of experimental tumors significantly (up to 80-90%) inhibits their growth, and at a dose of 1 mg / kg (both with intraperitoneal and oral administration) It has a growth inhibitory effect from 40 to 60%. That is, the antitumor effectiveness of the K-48 preparation is already apparent in small concentrations: for example, its use at a dose of 1 mg / kg orally amounts to ~ 1/10000 of its LD_{50}, which does not cause toxic effects [4,6].

As is known, in cancer patients, side effects of cytostatics are manifested, as a rule, in febrile neutropenia, which usually requires several days of hospitalization, the introduction of broad-spectrum antibiotics and hematopoietic growth factors [8,9,10]. Our studies show that the K-48 preparation can subsequently find application for the treatment of hemo- and immunodeficiency states that arise during the combined and complex treatment of malignant tumors in clinical practice.

Earlier, we presented data on the reduction of side effects in experimental animals when the K-48 preparation was combined with cytostatics such as taxol and etoposide on Ehrlich ascites carcinoma, as well as with cisplatin and cyclophosphamide on sarcoma-45 strain [3,5,18]. This study examined the effects of cisplatin and vincristine, either alone or in combination with K-48.

The aim of this work was to study the combined use of the cytostatics of cisplatin and vincristine with K-48 on an experimental tumor of sarcoma-180.

Materials and methods.

The object of the study was the K-48 drug developed at the *Republican Specialized Scientific and Practical Medical Center of Oncology and Radiology* of the Ministry of Health of the Republic of Uzbekistan, which was used together with cisplatin (Cisplatin Naprod, Naprod Life Scitnces Pvt / Ltd, India) and vincristine (Vincristine, Gideon Richter A.O., Hungary).

In the work, an experimental sarcoma-180 tumor was used, obtained from a bank of experimental tumor strains of the Russian Oncology Research Center, Russian Academy of Medical Sciences. After N.N. Blokhin. Tumors were inoculated to 42 BALB / c mice by subcutaneous injection of 30-60 mg suspension of tumor cells in 0.3-0.5 ml of 199 medium per animal. Treatment of animals was started 10 days after tumor implantation, the drugs were administered intraperitoneally daily for 8 days: cisplatin at a dose of 6 mg / kg and vincristine at a dose of 0.4 mg / kg. Then, half of the mice were injected orally at a dose of 1 mg / kg for 3 days with K-48. Slaughter was carried out 7 days after the last injection of the drug using cervical dislocation. The animals were kept in the vivarium of the *Republican Specialized Scientific and Practical Medical Center of Oncology and Radiology of the Ministry of Health of the Republic of Uzbekistan* on a standard diet.

Animals of the control group in an amount of 10, received physiological saline on the days of administration of drugs in the volume equivalent to the experimental groups. In 4 experimental groups there were 8 mice. When evaluating the antitumor effect, the mass and volume of the tumor were taken into account. To study the dynamics of tumor growth in animals of the experimental and control groups, tumors were measured in 3 projections at the beginning of the experiment and then every 5 days. Inhibition of tumor growth was calculated by the volume (V) and mass (M) of the recovered tumor. Before the experiment and at the end of the experiment, the body weight of the animals was determined, treatment tolerance was judged by the death of the animals, the spleen mass and leukocyte level were determined. Statistical data

processing was performed using the Statistica program, version 7.0.

The results of the study.

The study of the antitumor activity of cisplatin and vincristine, as well as their combination with the K-48 preparation on the sarcoma-180 strain, showed that vincristine (2 groups of mice) in a single dose of 0.4 mg / kg showed a growth inhibitory activity of 69.3 / 65, 2% (by volume and mass of V / M), however, it contributed to the death of 25.0% of animals, a decrease in spleen weight by 33.2%, body weight by 14.1% and a decrease in white blood cell count by 47.8% (Table 1)

In the 3rd group, after completion of treatment with vincristine, K-48 was administered, and the following results were obtained: the antitumor effect was 70.1 / 81.0% (V / M), which is 16.4% higher than the activity of vincristine by weight of tumors, animal body weight was 5.3% more than the original,

Table 1.

Study of the antitumor activity of vincristine and cisplatin in combination with K-48 in BALB / c mice using sarcoma-180 strain (treatment from 10 days after tumor inoculation)

Groups animals			% death	The mass of animals (g)		Weight spleen (g)	Volume tumors (cm^3)	Weight tumors (g)	% braking		leukocytes, 10^9l
				before beginning experience	after experience				V	M	
1	Control	n = 10	0	20.0 + 0.49	23.0 ± 0.39 *	0.3 ± 0.03	2.00 ± 0.21	3.18 ± 0.32	-	-	9.6 ± 0 9 4 *
2.	Vincristine 0.4 mg / kg	n = 8	25, 0	20.6 ± 0, 8 0	17.7 ± 0.50	0.2 ± 0.02 *	0.48 ± 0.05 *	1.10 ± 0.03 *	69, 3	65, 2	5.0 ± 0.66
3.	Vincristine 0.4 mg / kg + K-48 1 mg / kg	n = 8	0	24.6 ± 0.57	26.0 ± 0.70 *	0.4 ± 0.03 *	0.6 ± 0.09 *	0.6 ± 0.09 *	70, 1	81, 0	9.2 ± 0, 93 *
4.	Cisplatin 6 mg / kg	n = 8	3 7. 5	20.2 + 2.8 0	18.8 + 2.2 0	0.2 + 0.22	0.4 ± 0.09	0.5 ± 0.09 *	80, 2	84, 3	5.3 ± 0.96 *
5.	Cisplatin 6 mg / kg + K-48 1 mg / kg	n = 8	0	20.5 + 0.93	21.7 ± 0.88 *	0.4 + 0.03	0.3 ± 0.06 *	0.3 ± 0.05	85, 4	91, 5	8.8 ± 0.57

* p <0.05.

% inhibition of tumor growth was calculated by volume (V) and mass (M).

spleen - 33.1% more than the control group and the level of leukocytes was higher than in the 2nd group without K-48, but 5.8% lower than the control level.

When studying the antitumor activity of cisplatin on a sarcoma-180 strain in the 4th group, its high activity was shown to be 80.2 / 84.3% (V / M), however, the drug contributed to the death of 37.5% of the animals, reducing the body weight of animals by 7.0%. Moreover, the spleen mass was lower than in the control group by 30.4%, and the leukocyte level was 44.7% lower than the control.

At the same time, in the 5th group of animals with the subsequent administration of the drug K-48 after treatment with cisplatin, there was no death of the animals, but the antitumor activity increased by 5-7% and all side effects were reduced: for example, the body weight of the animals was 6.3% higher than the original, the spleen mass was higher than the control group by 32.9% and the leukocyte level was lower than the level of control animals by 8.3%.

CONCLUSION

A study of the activity of 2 drugs of cisplatin and vincristine on the tumor strain of sarcoma-180 in the late period after inoculation with an intraperitoneal 8-fold injection showed that the drugs show moderate activity of about 70-80% in volume and weight, but at the same time cause the death of some animals and exhibit a certain amount of side effects. It should be noted that the effect of cytostatic drugs on experimental tumors is more effective in the early period, 2-3 days after inoculation, than on already developed tumors [8, 9-17]. However, in clinical practice, treatment of malignant tumors with chemotherapeutic drugs, as a rule, is carried out with an already quite pronounced tumor process, when a combination of several types of antitumor therapy is necessary.

In our studies, the combined use of known cytostatics with the new K-48 drug increases their own growth inhibitory activity, while reducing the toxic effects of the treatment. In addition, this combined use

of chemotherapeutic agents with a new derivative of colchamine eliminated the death of experimental animals caused by their toxic effects and reduced such side effects as weight loss and spleen, as well as increased white blood cell count. Thus, a new class of analogs of colchicine and colchamine, demonstrates a number of interesting features, which include combining the antitumor effect with a stimulating effect on the hematopoiesis, which can subsequently be used in clinical practice in the treatment of hemotoxicity of antitumor therapy.

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MODIFICATION OF TOXIC ACTION OF KNOWN CYTOSTATICS BY THE COMBINED APPLICATION OF A NEW DERIVATIVE COLCHAMIN K-48 ON STRAIN OF SARCOMA-45

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SUMMARY

A study of the antitumor activity of cisplatin and cyclophosphamide in an experiment on the tumor strain of sarcoma-45 in the late period after inoculation showed that the preparations show moderate activity from 60 to 80%, but a number of serious side effects are revealed in animals. The combined use of these drugs with a new derivative of colchamine - K-48, which has an immunomodulating effect and stimulates the proliferation of hematopoietic progenitor cells in the experiment, leads to a decrease in their toxic effects and also increases antitumor activity.

Key words: antitumor activity, chemotherapy toxicity, colchamine derivative, hematopoietic stem cells, sarcoma-45.

The use of chemotherapy in the treatment of malignant tumors inevitably leads to the development of various toxic effects in patients. Most chemotherapeutic drugs, acting cyclically, maximize the damaging effect on rapidly dividing cells. In addition to tumor cells, normal tissue cells with high regenerative activity, in particular blood cells and bone marrow, fall into this category. With malignant growth, an imbalance develops between the intensity of production of antioxidant enzymes and free radical oxidation, as well as the level of functional activity of the antioxidant defense system [7,8,10]. Side effects of hematotoxic effects of cytostatics are well known, treatment of febrile neutropenia caused by them leads to an increase in hospitalization, and also necessitates the use of broad-spectrum antibiotics and hematopoietic growth factors. All this leads to both a deterioration in the quality of life of cancer patients and an increase in economic costs for overcoming the hematological toxicity of the therapy [8.9]. In this regard, the low-toxic derivatives of colchicine and colchamine, which can be inducers of cytokines and cause processes in the body leading to proliferation of hematopoietic progenitor cells [1,2,3], created in the laboratory of antitumor drugs RSNPMTSOiR MZ RUz, are of interest.

When studying the biological effect of a number of derivatives of colchicine and colchamine with low toxicity and high antitumor activity, effective compounds were found that experimentally stimulate the development of colony forming units in the spleen (CFU), giving rise to granulocyte, monocytic, erythroid, megakaryocytic and lymphoid colonies in sublethal doses of mice. The stimulating effect of the studied compounds is manifested in small doses of the administered drug (1 mg / kg), a further increase in their dosages, as a rule, leads to a decrease in the formation of CFUs. When using these substances in therapeutic doses, any pronounced toxic effects are not manifested [2,4].

Another important circumstance is that some of these compounds, even in small doses, can inhibit the growth of various experimental tumor strains, while the use of certain known immunomodulators can cause the progression of tumor growth. In addition, the use of these drugs in small doses for oral administration in experimental animals does not lead to the development of toxic effects. So, the dose of K-48 1 mg / kg is ~ 1/1000 of its LD50, which can subsequently be used for the correction of hemo- and immunodeficiency states that arise during treatment of malignant tumors with radiation and chemotherapeutic methods [2,3].

Thus, the domestic drugs developed from plant alkaloids, in particular K-48 [1,5], developed at *Republican Specialized Scientific and Practical Medical Center of Oncology and Radiology of the Ministry of Health of the Republic of Uzbekistan*, have a multifactorial biological effect - both direct cytotoxic and the ability to restore hematopoiesis in laboratory animals [2,3] . At the same time, the cost of the stages of production of these compounds is much less than the synthetic (recombinant) GM-CSF inductors. If the protective effect of the K-48 preparation on the organism of experimental animals from radiation exposure, as well as from the use of such well-known chemotherapeutic agents as taxol, etoposide, and doxirubicin [1,4,16] was previously shown, then this effect is shown in an experiment on animals with sarcoma 45 treated with cisplatin and cyclophosphamide.

The aim of this work was to study the combined use of the known cytostatics of cisplatin and cyclophosphamide with a new derivative of colchamine K-48.

Materials and methods. The object of the study was the K-48 preparation developed at the *Republican Specialized Scientific and Practical Medical Center of Oncology* of the Ministry of Health of the Republic of Uzbekistan, which was used together with cisplatin (Cisplatin Naprod, Naprod Life Scitnces Pvt / Ltd,