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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,

India) and cyclophosphamide (cyclophosphamide-Getwell, Getwell Pharmaceuticals, India).

An experimental tumor was used - sarcoma 45, obtained from a bank of experimental tumor strains of the Russian Oncology Research Center, Russian Academy of Medical Sciences. N.N. Blokhina. Inoculation of the tumor strain to 42 white outbred rats was carried out according to generally accepted methods: the tumor was inoculated subcutaneously with a suspension of tumor cells of 30-60 mg in 0.3-0.5 ml of 199 medium per animal [8,10-12,18-20]. Treatment of animals was started 14 days after tumor implantation. Cisplatin was administered to rats at a dose of 6 mg / kg, cyclophosphamide at a dose of 9 mg / kg for 8 days intraperitoneally. After that, half of the animals 3 times daily at a dose of 1 mg / kg was orally administered K-48. Slaughter was carried out 7 days after the last injection of the drug. 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, Tashkent* on a standard diet.

Animals of the control group in an amount of 10, received physiological saline on the days of drug administration in the experimental groups in the same volume as the studied drugs. In 4 experimental groups there were 8 rats. 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 three 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 extracted tumor [6,14,17]. Before the introduction and at the end of the experiment, the body weight of the animals was determined, the tolerance of treatment was judged by the death of rats, the weight of the spleen and the level of leukocytes were determined. Statistical data processing was performed using the Statistica program, version 7.0.

Research results and discussion. The study of the antitumor activity of the studied drugs on the sarcoma-45 strain showed that cisplatin (group 2) in a single dose of 6 mg / kg, applied 14 days after inoculation, showed antitumor activity of 59.1 / 60.2% (V / M), however, the drug contributed to the death of 25.0% of animals, a decrease in spleen mass by 31.3%, body weight by 18.4% and a decrease in white blood cell count by 39.6% (Table 1).

In the 3rd group, to which K-48 was administered after cisplatin, the following results were obtained: the antitumor effect was 78.6 / 68.3%, which is 19.2 / 8.1% more than in the group without K- 48, the animal body weight was 5.2% higher than the initial one, the spleen was 17.1% higher than the control group and the leukocyte level was higher than in the 2nd group, but 8.3% lower than the control level.

Table 1.

Antitumor activity of cisplatin and cyclophosphamide in combination with K-48 in white outbred rats on sarcoma strain -45 (treatment on day 14 after tumor inoculation)

Groups animals			% death	Weight animals (g)		Tumor volume (cm^3)			Tumor mass (g)	Weight spleen (mg)	% braking		Leuko- cytes , 10^9l
				before experience	after experience	14 day	19 day	29 day			V	M	
1.	Control	n = 10	0	110.0 + 7.1	105.0 ± 10.0 *	19.2 + 4.2	38.5 + 16.0	46.0 + 12.0	20.3 + 5.2	364.0 + 22.0	-	-	7, 2 +0.3
2.	Cisplatin 6 mg / kg	n = 8	25.0	100.0 + 4.1	76.0 + 7.0	15.6 + 4.3 *	13.2 + 3.6	19.0 + 7.0	8.0 + 2.8 *	251.3 + 21.8	59.1	60, 2	4.4 + 0.5 *
3.	Cisplatin 6 mg / kg + K-48 1 m g / kg	n = 8	0	92.6 + 3.2	97.3 + 3.8 *	15.8 + 4.4	13.1 + 2.8 *	10.0 + 3.9 *	6.5 + 2.9	427.0 + 70, 2 *	78.6	68.3	6.6 + 0.3
4.	Cyclophosfan 9 mg / kg	n = 8	50 , 0	90.0 + 0.1	60.7 + 17.0 *	38.5 + 16.0	10.5 + 2.0 *	7.3 + 2.7	4.9 + 1.6 *	325.0 + 125, 1	84.0	76, 4	5.6 + 0.6 *
five.	Cyclophosfan 9 mg / kg + K-48 1 mg / kg	n = 8	0	92.0 + 1.2	96.0 + 2.7	16.8 + 3.0 *	10.7 + 2.2	5.3 + 1.2	3.9 + 0.7	420.0 + 80.0 *	88.5	81.2	7.0 + 0.2

* p <0.05 .

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

When studying the antitumor activity of cyclophosphamide, its high activity was shown to be 84.0 / 76.4%, however, the drug contributed to the death of half of the animals and to a decrease in body weight of rats by 33.7%. Moreover, the spleen mass was lower than in the control by 10.7%, and the leukocyte level was lower by 22.2%.

At the same time, in the 5th group, when K-48 was added to cyclophosphamide, no animal deaths were noted, but the antitumor activity increased by 5.0% and all side effects were reduced. The body mass of rats was 4.1% more than the original, the spleen mass was 14.7% higher than the control, and the leukocyte level was at the level of the values of the control animals.

CONCLUSION

Thus, a study of the activity of cisplatin and cyclophosphamide on the tumor strain of sarcoma-45 in the late period after inoculation with 8-fold intraperitoneal administration showed that these drugs exhibit moderate activity of about 60-80%, but their use causes various side effects. It should be noted that the effect of various cytostatics on the developed tumors, as a rule, is not so successful in comparison with their effect on the tumors in the early period of their development (at the start of treatment 2-3 days after inoculation) [8, 9,13,15]. In oncological practice, the chemotherapeutic effect on human malignant tumors is often carried out in the late stages of their development, when a combination of different types of antitumor therapy is necessary. Studies have shown that the combined use of the new derivative of colchamine K-48 markedly increased the antitumor activity of known cytostatics, and also eliminated the toxic effects caused by them, such as death of animals, decrease in body weight and spleen, decrease in the level of leukocytes, which allows us to recommend it for further research, as a promising low-toxic antitumor drug with an interesting mechanism of biological action.

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ЭКОЛОГИЧЕСКИЕ ПРОБЛЕМЫ РАЗВИВАЮЩИХСЯ СТРАН

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АННОТАЦИЯ

Развивающиеся страны определяются как группа государств, которые не улучшили эксплуатацию человеческих и природных богатств, содержащихся в них в максимально возможной степени, она также страдает от нехватки своих основных услуг, таких как образование и здравоохранение, где проживает приблизительно семьдесят процентов от общего населения мира, а сельскохозяйственное производство составляет долю в тридцать пять процентов от общего мирового производства, в то время как промышленное производство эквивалентно семи процентам мирового производства.

ANNOTATION

Global environmental problems also affect primarily developing countries. For example, the most difficult problem to solve is global climate change, which primarily concerns developing countries.Problems associated with poor health as a result of environmental pollution are compounded by increasing negative impacts from industrial and agricultural activities. This leads, among other things, to an increase in both the relative and absolute number of people affected by occupational diseases.

Ключевые слова: Экология, внешние факторы, развивающиеся страны, экологический кризис.

Keyword: Ecology, external factors, developing countries, environmental crisis.

Охрана природы;

одна из наиболее злободневных проблем современности, в той или иной степени, с ней столкнулись все страны мира. Проблема взаимоотношения общества и природы одна из самых острых проблем, очевидным является то обстоятельство, что главными причинами усиливающегося антропогенного воздействия на окружающую среду служит рост населения и возрастание масштабов потребления природных ресурсов, промышленного и сельскохозяйственного производства.

В мире сегодня от 25% до 33% всех зарегистрированных заболеваний, по оценкам ВОЗ, напрямую связаны с загрязнением окружающей среды, из них 2/3 составляют дети. Ежегодно 3 млн. детей, не достигших пятилетнего возраста, становятся жертвами неблагоприятных факторов окружающей среды.