The Role of Complement in the Treatment of Tumor Diseases

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***Abstract*—The phenomenon of antibody is dependent on the cell in which occurs the main mechanism of action of all targeted antitumor preparations containing monoclonal or polyclonal antibodies. Successful manifestation of this phenomenon is possible only with the correct ratio between the antigens of cancer cells, antibodies specific to them and the required amount of complement. The following paper shows the need to monitor the quantitative content of complement in the patient's serum and correct its content by introducing the required volume of fresh frozen plasma as a source of exogenous complement. The required amount of specific antibodies (dosage of the drug) must be determined after proper correction of the amount of complement in the patient's blood. If this condition is met, the maximum efficacy of the drug and the increased success of the treatment of tumor diseases will be achieved.**

***Index Terms*—complement, antibody, antitumor activity, serum**

I. Introduction

It is known that the active molecules of all targeted antitumor drugs are monoclonal or polyclonal antibodies, i.e."targeted" to antigens of cancer cells. The basis of the action of all targeted drugs is the well-known phenomenon of the antibody, the complement of dependent lysis of abnormal cells. For successful destruction of tumor cells, the interaction of three "participants" of the process of selective lysis is necessary. First, these are antigens (receptors, markers) associated with the cell surface of abnormal cells. Secondly, these are antibodies specific for tumor cell antigens. And thirdly, this complement is a non-specific enzyme that destroys any cells, on the surface of which there are antibodies specific for cellular antigens. The effectiveness of the treatment of cancer with targeted drugs depends on the density of antigens on the cell surface of cancer cells, a sufficient amount (titer) of antibodies specific to the pathological antigens and the required concentration of complement molecules in the blood serum [1], [2].

The number of pathological antigens on the surface of tumor cells may be different - there are quite a lot of them in aggressive forms of cancer, and they are fewer in cells of slow-moving types of diseases. The concentration of antibodies specific for tumor antigens can be adjusted by changing the dosage of the drug used. The content of complement and its activity in the blood of patients varies and depends on the physiological characteristics of the organism and, moreover, on the presence of autoimmune diseases (allergy, collagenosis, etc.) at which the concentration of complement is markedly reduced. The low content of complement in the patient's blood or its low activity may disrupt the required ratio between the "participants" of the antibody phenomenon and the complement of dependent lysis and reduce the effectiveness of treatment with targeted, antitumor drugs. However, the role of complement in the treatment of tumor diseases with targeted drugs remains outside the area of interest of practicing oncologists. The purpose of this work is to study the effect of the amount of complement in the serum of recipients on the antitumor activity of targeted drugs [3], [4]. This goal is achieved by comparing the therapeutic efficacy of the antitumor targeted drug "Normogen" at various concentrations of complement in the serum of recipients.

II. Results and Discussion

Outbred laboratory rats weighing 150–170 grams were used in studies of the antitumor activity of the targeted prepreg "Normogen". In the experiment, 20 rats were used, which were divided into two, groups – the "control" group and the "experimental" group, both groups equal in the number of animals.

To induce a tumor process in rats, 100,000 cells of a laboratory strain of an ovarian affinity tumor of rats (OAfT) tropically to lung tissue were intravenously injected. After three days, 0.5 ml of a 0.1% solution of the Normogen preparation in 0.9% NaCl was injected into the tail vein in rats from the experimental group. After 15 days from the time of the introduction of OAfT tumor cells, the rats of the control and experimental groups were killed, and their lungs were examined for the presence of OAfT solid clones. The results of the experiment are shown in Fig. 1 and Fig. 2.

Fig. 1 shows the lungs of 10 rats from the control group. The photograph shows that the lung tissue of all

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the rats in the control group is affected by multiple clones of the solid tumor of OAfT.

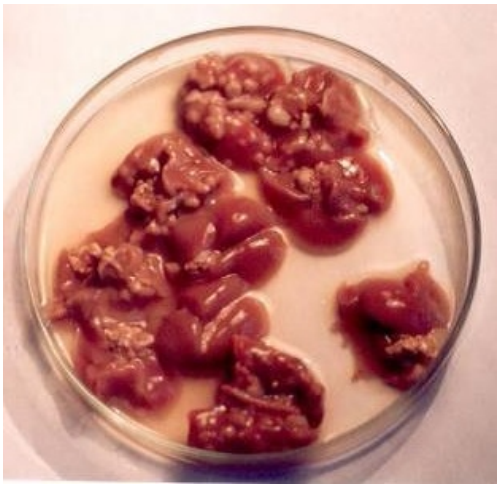

Figure 1. Lungs rats of the control group. 100% damage to the tissues of the lung clones of a solid tumor of OAfT.

Fig. 2 shows the lungs of 10 rats from the experimental group, who were intravenously injected with a solution of the Normogen preparation for 14 days.

The photograph in Fig. 2 shows that more than 60% of rats' lungs are free of OAfT clones. While 40% of the lungs of animals remained affected by multiple clones of the tumor.

Figure 2. Lungs rats of the experimental group. 60% of rat lungs free from tumor clones after use of the drug "Normogen".

Analyzing the reasons for such different results of the therapeutic effect of the drug "Normogen" on the course of the tumor process in rats of the experimental group, the following conclusions were made. The basis of the therapeutic effect of the drug "Normogen" is the phenomenon of antibody-complement dependent tumor cell lysis.

Due to the fact that the amount of antibodies of the "Normogen" preparation, administered intravenously, as well as the number of cells of OAfT injected, was the same for all animals of the experimental group, it became necessary to analyze the content of complement in the blood serum of rats.

The study of the content of complement in the serum of a large number of rats and mice not engaged in the experiments showed a significant difference in the content of this most important component of humoral immunity in the organisms of intact animals.

In connection with a possible difference in the content of complement in the blood serum of animals, it became necessary to study the antitumor effect of the drug "Normogen" in combination with exogenous complement (replacement therapy).

As a source of exogenous complement, dry, lyophilized serum of guinea pig produced by "Vektor" (Russia) was used, which was dissolved in physiological saline and injected into rats at the same time as Normogen.

The result of the antitumor effect of the drug "Normogen" in combination with exogenous complement is shown in Fig. 3.

The conditions of the study on the effect of correction of complement content in the serum of 10 rats on the antitumor activity of the "Normogen" preparation were similar to the conditions when studying its effect on rat ovarian affinity tumor cells in previous experiments.

From the data of Fig. 3 it can be seen that an increase in the complement content in the blood of rats leads to an almost complete (96%) cure of animals from solid tumors of ApoIa, which can be seen even by the natural color of the lung tissue. It is possible to achieve a complete cure of animals from AFNF tumors with longer treatment with the "Normogen" preparation.

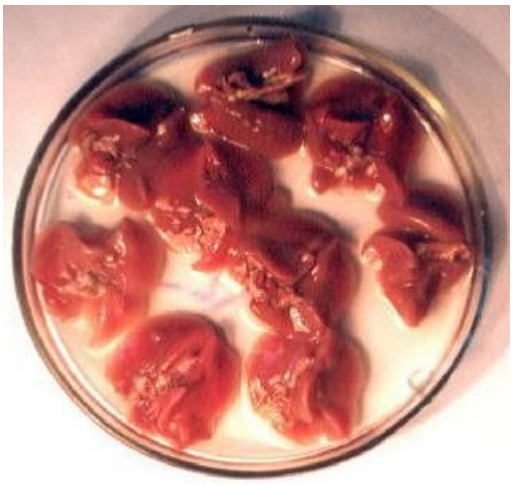

Figure 3. Almost complete (96%) recovery of animals from OAfT with the "Normogen" preparation in combination with exogenous complement.

The work was carried out in triplicate, with the same end result. Studies have shown the decisive role of the concentration and activity of complement in the blood serum of animals, on the effectiveness of the treatment of tumor disease with antibodies of the targeted antitumor drug "Normogen".

The obtained results of the effect of complement concentration in the blood serum of animals on the effectiveness of targeted therapy with the antitumor drug "Normogen" became the basis for studying the effect of

the amount of complement in the patients' blood serum on the results of therapy with the "Normogen" drug.

The study involved well-informed volunteer patients with stage IV of the disease, who were already denied specialized treatment because of the advanced tumor process.

In all patients who participated in the clinical trials of the "Normogen" preparation, the diagnosis was verified by histological or cytological methods. Previously, all patients received specific treatment in accordance with the diagnosis of the disease - surgical treatment in combination with chemotherapy or radiation therapy. The interval between the previously conducted specific antitumor therapy and therapy of the patient with the drug "Normogen" was not less than two months.

The drug "Normogen" was administered to patients daily intravenously, drip, - at 1, 2, 3 days at a dose of 300mg. at 4,5,6 and 7 days at 200mg. drip, intravenously. On the 3rd, 5th and 7th day from the beginning of the therapy with the "Normogen" preparation, the patients were administered 250ml. each of the same, according to the patient's blood group, fresh frozen plasma containing complement.

Subsequently, it is known that the main part of the subunits of the complement is synthesized in the liver, then any disease of this organ leads to a decrease in the concentration and activity of complement in the blood serum, which reduces the ability of the patient to fight the tumor disease and contributes to the progression of the cancer process.

In this regard, the study of the dynamics of changes in the amount of complement in the serum of patients with liver cancer was of the greatest interest.

The work was carried out with patients with a verified diagnosis of liver cancer, with a relatively satisfactory condition - on the WHO scale, no more than 3 points (with disabilities), whose quality of life corresponded to less than 70 - 80% on the Karnovsky scale.

In the course of the work, the effect of the amount of complement in the blood of liver cancer patients on the effectiveness of treating patients with Normogen, in monotherapy, was studied.

It was found that the complement content in the serum of patients with liver cancer is significantly reduced, and is 60-40% of the norm.

The introduction of fresh frozen plasma increased the content of complement in the blood, which never reached the indices of the physiological norm, due to its intensive expenditure in the process of selective lysis of tumor cells.

After completion of the course of treatment, the condition of the majority of patients improved, they became more active, and less time was spent on bed rest. Patients who received fresh frozen plasma showed improvement in overall health, well-being and reduction of pain.

The treatment of patients with the Normogen preparation in combination with fresh frozen plasma (source of exogenous complement) resulted in the stabilization of the tumor process in most patients being achieved, with small (up to 25%) regression in tumor sizes and metastases. In some cases (generalization of the oncological process), the use of fresh frozen plasma did not give a positive result.

Fig. 4 shows the dynamics of changes in the amount of complement with a small (up to 25%) regression of tumor size and its metastases.

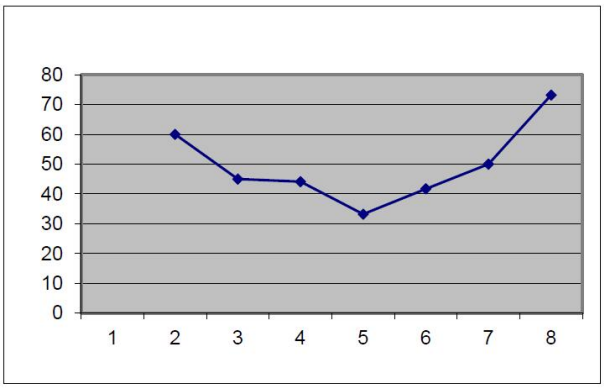

Figure 4. Dynamics of changes in the amount of complement in serum during regression of the tumor and its metastases.

Table I shows the dynamics of changes in the amount of complement in serum during regression of the tumor and its metastases by day.

TABLE I. DYNAMICS OF CHANGES IN THE AMOUNT OF COMPLEMENT IN SERUM DURING TUMOR REGRESSION BY DAY

№	Full name	Quantity complement by day, (%)	
		days	%
1	Б.	1	-
		2	60,0
		3	45,0
		4	44,0
		5	33,0
		6	42,0
		7	50,0
		8	73,0

Fig. 5 shows the dynamic change in the amount of complement in the serum with the stabilization of the tumor process.

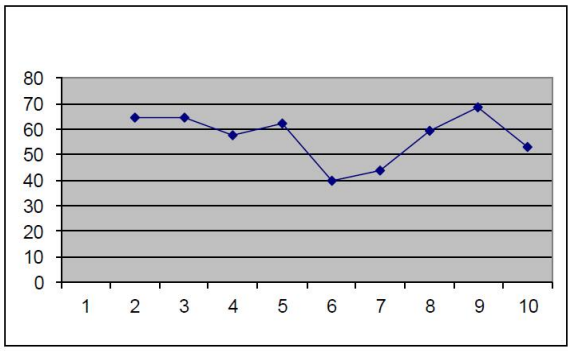

Figure 5. Dynamics of changes in the amount of complement in the blood serum during the stabilization of the tumor process.

Table II shows the results of changes in the amount of blood in the blood serum with the stabilization of the tumor process by day.

TABLE II. DYNAMICS OF CHANGES IN THE AMOUNT OF COMPLEMENT IN THE SERUM DURING THE STABILIZATION OF THE TUMOR PROCESS BY DAY

№	Full name	Quantity complement by day, (%)	
		days	%
2	У.	1	-
		2	64,0
		3	64,9
		4	57,0
		5	62,0
		6	40,0
		7	43,0
		8	59,0
		9	68,9
		10	53,0

Fig. 6 shows the changes in the dynamics of the amount of complement in the patient's serum at the terminal stage of the disease.

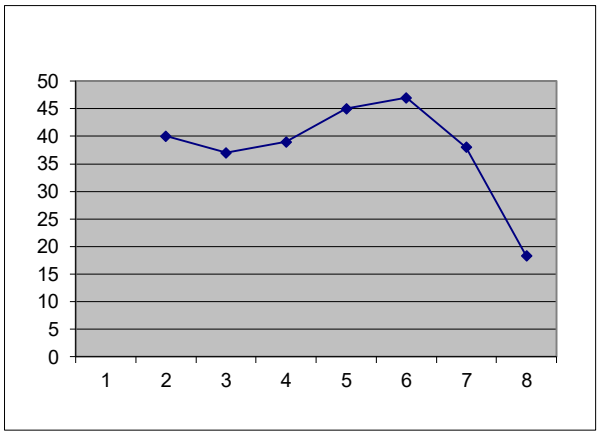

Figure 6. Dynamics of changes in the amount of complement in the patient's serum at the terminal stage of the disease.

The results of changes in the dynamics of the number of complement in the serum of the patient at the terminal stage of the disease by day are shown in Table III.

TABLE III. DYNAMICS OF CHANGES IN THE AMOUNT OF COMPLEMENT IN THE PATIENT'S SERUM AT THE TERMINAL STAGE OF THE DISEASE BY DAY

№	Full name	Quantity complement by day, (%)	
		days	%
3	C.	1	-
		2	40,0
		3	37,0
		4	39,0
		5	45,0
		6	47,0
		7	38,0
		8	18,5

The identity of the mechanism of the antitumor action of all targeted drugs suggests that it is necessary to monitor and correct the content of complement in the blood serum of patients in order to obtain greater efficacy of treatment [5], [6].

However, the use of fresh frozen plasma is not included in the standards for the treatment of neoplastic diseases. Moreover, the method of enhancing the antitumor activity of targeted drugs by correcting the content of complement in the patient's serum is not considered by oncological science and practicing doctors.

III. CONCLUSIONS

In conclusion the study of the role of complement in targeted therapy of tumor diseases with monoclonal or polyclonal antibodies showed the importance of observing quantitative ratios between the antibodies used and the complement in order to realize the antibody phenomenon — the complement dependent cancer cell lysis. In most cases, the complement content in serum of cancer patients is reduced, which is the limiting factor for the successful use of targeted drugs. Correction of the amount of complement in the patient's serum by administering the required amount of exogenous complement is thus a necessary condition when treating any tumor diseases with targeted drugs.

In our opinion, it is necessary to revise the protocols for the treatment of tumor diseases and to include, if necessary, correction of the content of complement in the patient's blood serum.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

A. P. Frantsev conducted an analysis of the results of the therapeutic effect of the drug “Normogen” on the influence of the tumor process in rats of the experimental group. U. M. Datkhayev conducted general management and studied the effect of the amount of complement in the blood of patients with liver cancer on the effectiveness of treatment of patients with the drug “Normogen”. J. K. Ukibayev worked on statistical processing of the results obtained and the design of the article. The research was organized and edited by D.A Myrzakozha. All authors had approved the final version.

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