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Review Article

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Extracorporeal Immunotherapy in Oncology

Voinov VA*, Orlov SV, Karchevskii KS and Isaulov OV

Apheresis Therapy Department, Pavlov First St. Petersburg State Medical University, Russia

***Corresponding author:**
Dr. Valery A Voinov, Head of the therapeutic apheresis Department of Gravitational blood surgery, Pulmonology clinic of I.P. Pavlov First Saint-Petersburg State Medical University, 4/6 Leo Tolstoy Str. 12, 197022 Saint-Petersburg, Russia, Tel: +79119126502; E-mail: voinof@mail.ru

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Abstract

Tumors development is closely related to the immune system state and in immunosuppression tumors occur many times more often. The quality of the immune defense depends on how the recognition system functions for malignized tumor cells and its timely destruction. However, the immunosuppression state may be a result of the tumor process itself. The tumor itself generates soluble molecules that inhibit the killer activity of lymphocytes and macrophages, which allows tumor cells to survive in the body. Therefore, it is justified to perform apheresis therapy aimed at removal of such inhibitors, and targeted restoration of cytotoxic activity of leukocytes, which should contribute to the tumor cells apoptosis. This method of extracorporeal immunopharmacotherapy is indicated not only in far-advanced cases, but also after any radical operations, when metastases are not detected and even chemotherapy is not carried out.

Keywords: Tumor, Immunosuppression, Leukocytes Cytotoxic Activity, Plasmapheresis, Extracorporeal Immunotherapy

Introduction

Over the past 30 years WHO experts report very disappointing statistics of a twofold increase in the number of patients with malignant tumors. This threatens to double by 2020 and triple by 2030. In Germany, for example, currently about a quarter of men and 20% of women die from cancer, and estimates show that approximately 51% of men and 43% of women will develop cancer during their lifetime [1]. However, effectiveness of their treatment remains unsatisfactory. To date, there are more than 100 cytotoxic drugs used, the marketing of which achieves $42 billion [2]. The main obstacle in the successful treatment of cancer is dangerous chemotherapy side effects, which worsens the quality of life of the cancer patient [3]. All this makes us look for new ways to treat cancer.

The immune system role in oncogenesis

Tumors development itself is closely related to the immunity state. In immunodeficiency, tumors occur 100-1000 times more often than in the general population [4]. One of the main factors is decreased activity of the cellular immunity. And normally a person constantly develops cells with a different antigenic structure. They are diagnosed and removed by cytotoxic and killer T-lymphocytes. But when the latter are unable to cause apoptosis of the tumor cells that have appeared, there are conditions created for their subsequent extensive growth and spread [5].

And the tumor process itself contributes to immunosuppression, especially considering development of concomitant endogenous cancer intoxication. In addition, surgery with inevitable stress contributes to immunosuppression within 2-4 weeks after it. Moreover, all types of chemo- and radiation therapy also lead to secondary immunodeficiency – reduced number of T-lymphocytes, which are important in the tumor cells destruction. Therefore, attempts are made to use the chimeric antigenic receptors to enhance the T-cells activity [6,7]. However, while for B-cell tumors in hematology the use of such manipulation was quite effective, the solid tumors were found to be less susceptible [8,9]. The reason is that the tumor itself can reduce the metabolic activity of T-cells [10,11].

For a long time, such patients have been found to have soluble circulating protein substances with relative molecular weight of 70-150 thousand Daltons, inhibiting the killer activity of lymphocytes and macrophages, and even contributing to their apoptosis, which allows tumor cells to survive in the body [12]. It is believed that the tumor cells themselves are the producers of such inhibitors. One of the possible mechanisms of their action is inhibition of cytolytic activity of tumor necrosis factor (TNF-α) and other cytokines (IL-1, IL-6), aimed at the tumor cells destruction [13]. At the same time, it becomes obvious that using these cytokines (TNF-α) as a therapeutic agent even in high doses a significant clinical effect cannot be achieved and their general toxic effect can be accompanied by additional complications.

Obviously, this is why despite advances in cell cultures tumor growth control *in vitro* or in mice, immunotherapy in patients with malignant tumors does not provide the desired results [14,15]. It is the presence of circulating inhibitors that is likely to limit the therapeutic effect of various anti-tumor vaccines and cytotoxic cells activated by various

methods, in particular lymphokine-activated cells (LAC-cells), etc.

Anti-tumor immunotherapy

In such a situation, plasmapheresis may be the only pathogenetically justified treatment, aimed at removing molecules that inhibit the cytotoxic activity of lymphocytes. And indeed, such a concept has been confirmed in experiments on 6 dogs with induced breast tumors and osteosarcoma, when after five procedures the tumors regressed, the residual tumor tissues were resected and within the next 1-4 years until the natural death of these animals, there were no recurrences of tumors. This approach was also tested in clinical practice in 16 patients with various types of malignant tumors, the treatment of which all other conventional methods of treatment were not effective. Cascade plasmapheresis was performed in the volume of 5-25 ml/kg of the body weight with adequate replacement of high-molecular fraction of the patient's plasma with a similar fraction produced by cascade filtration of donor plasma, 3 times a week and in the total amount of 12 such procedures within a month. This made it possible to achieve a pronounced clinical effect in 14 of these patients, which was followed by disappearance of pain, decrease in the size of the tumors and their metastases and signs of tumor cell necrosis in histological examination. In three patients complete lysis and tumor tissue necrosis were observed, in six cases the tumor size decreased by 50% and more, and in three cases the tumor size decreased by less than 50%, and in the rest patients there was only tumor stabilization observed [16]. Earlier studies have also shown the efficacy of apheresis of such cellular immunity inhibitors in the treatment of tumors of the mammary gland, kidney, prostate gland, non-small cell lung carcinoma, ovarian cancer, and other sites [17].

However, given detection of such inhibitors not only in the blood, but also in the ascitic fluid and even in the urine, it can be assumed that they are not completely removed by cascade filtration. Therefore, it can be assumed that conventional plasmapheresis in amount of up to half of the circulating plasma volume (CPV) and in the same intensive plasma replacement mode is able to provide a more complete removal of such inhibitors of anticancer protection natural mechanisms, together with other components of endotoxicosis and in combination with surgical and chemo-radiation exposure methods to provide more promising results in the treatment of cancer patients. And only after removal of these inhibitors we can expect a more complete effect of cellular antitumor immunity stimulation. This hypothesis is also supported by W. Kuang et al [18].

Nevertheless, it seems to us that for a more complete and reliable effect it is advisable to further excite the cytotoxic activity of lymphocytes. Therefore, we have developed a Protocol of intensive apheresis therapy of cancer patients - up to 8 procedures of plasmapheresis with removal of 0.5 CPV each time with replacement by donor plasma in a ratio of 0.8:1. Only after 5-6 procedures of plasma exchange we carry out incubation of leucocytes isolated during plasmapheresis with interleukins (IL-2 – *Roncoleukin* 500 mg or IL-1β - *Beta-leukin* 0.001 mg) in a thermostat for three hours with subsequent return to the patients [19]. According to this scheme, 10 patients with non-small cell lung carcinoma were treated. Diffuse lung disease does not allow surgical treatment, and using only chemotherapy, their life expectancy does not exceed half a year. The preliminary results (almost twofold increase in levels of TNF-α, IL-2 and IFN-γ and increase in life expectancy from 0.5 to 2-2.5 years) can be considered encouraging (Table 1).

Table 1: Cytokine levels in cancer patients (n = 10)

Stage	TNF-α picogram/ml	IL-2 picogram/ml	IFN-γ picogram/ml
Initial level	15.2±2.4	19.5±2.1	36.6±4.1
After plasma exchange	23.3±3.3*	42.2±3.9*	28.8±3.4
After lymphocytes incubation	34.6±4.2*	49.6±4.2*	75.4±5.8*

Note: * - changes from baseline are significant (P<0.05)

It should be noted that the level of IFN-γ after the course of plasmapheresis decreased. This is due to its temporary real leaching, but after an additional course of plasmocyte apheresis with incubation of lymphocytes with *Beta-leukin* or *Roncoleukin*, its significant rise was observed. The increase in the levels of TNF-α and IL-2 immediately after plasma exchange could be explained by unblocking of lymphocyte receptors after removal of their killer activity inhibitors. This continued after their incubation with interleukins.

A known limitation of apheresis therapy in cancer patients may be its relatively high cost. However, alternative methods of cytotoxic effects correction may be more expensive and more dangerous to the health.

Conclusion

The presented material clearly shows both the increased frequency of tumor diseases in the world and insufficient efficiency of all the methods used for their treatment – from surgical, to radio- and chemotherapy. In itself, the tumor process is accompanied by intoxication, and the drugs used only further enhance it. Increasing endotoxicosis plays the leading role in thanatogenesis.

Taking into account the significant role of immune disorders at the stage of a tumor appearance, formation and further progressive growth, there is an increased importance of extracorporeal immunotherapy methods, aimed at removing inhibitors of lymphocytes killer activity and at excitation of their cytotoxic properties. Such methods will also be justified in cases of radical removal of tumors in the absence of visible metastases. It is almost impossible to guarantee the absence of some tumor cells left in the surrounding or distant tissues, so in such cases it is justified to use the methods of extracorporeal immunotherapy both to remove the remaining molecules-inhibitors of the lymphocytes killer activity and to restore their cytotoxic activity, which gives a great guarantee of recurrence prevention.

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