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Review Article

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Therapeutic Apheresis in Oncology

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Abstract

Background: *Given the steady growth of oncologic diseases incidence worldwide, their treatment still remains not effective enough. The used methods of radio- and chemotherapy are associated with severe intoxication, underlying thanatogenesis. Besides, the tumor process is also associated with increasing intoxication.*

Objective: *To study pathogenesis of tumor endotoxemia, radio- and chemotherapy complications, and to discover possibilities to use extracorporeal methods of detoxification and immune correction in treatment of malignant tumors.*

Method: *To review the world literature concerning tumor conditions treatment complications and methods of their correction; to use own methods of extracorporeal detoxification and immune correction.*

Results: *WHO reports present rather discouraging findings about a significant increase of patients with malignant tumors for the last 30 years and remaining rather high level of death rate. Using plasmapheresis weekly during the course of radiotherapy for pancreatic cancer was able to prevent a lot of complications and continue the treatment. There is a report about using plasmapheresis with lymphocytes isolation ant their incubation with roncoleukin (IL-2) in patients with small-cell carcinoma of the lungs. They show a significant increase of IL-2, TNFα, and interferon serum concentration in the patients, and their survival rare increased from 0.5 to 2-2.5 years.*

Conclusion: *Extracorporeal detoxification and immune correction can help eliminate endotoxemia and improve the treatment outcome. At the same time, higher doses of chemotherapeutic agents can be used.*

Keywords: Cancer Endotoxemia, Chemotherapy Complications, Detoxification, Plasmapheresis, Hemosorption, Extracorporeal Immunotherapy.

Introduction

WHO experts show very unfavorable statistics of double increase in number of patients with malignant tumors for the last 30 years that is to double by 2020 and triple by 2030. In Germany, for example, currently about a quarter of males and 20% of females die from cancer, and the estimates show that about 51% of males and 43% of females will develop cancer during their lifetime. By 2030, prostate, lung, breast and liver cancers will be the most common ones [1]. Annually breast cancer affects more than 1 million women worldwide [2]. In the USA, by 2030, the number of cancer patients will increase from 1.6 million to 2.3 million, mainly due to older people [3]. In Japan, given the highest life expectancy, tumors are the leading cause of death. And since older people have a number of other chronic diseases, tumor chemotherapy complications are also increasing [4]. And considering the high mortality rate of such patients, it further emphasize the urgency of this issue.

Pathogenesis of tumor endotoxemia

Development of a tumor is followed by production and accumulation of a number of pathological metabolites, which substantially cause asthenization of patients, dystrophy and the increasing cachexia. Cancer intoxication is one of the endogenous types of intoxication. Increase of filtrate nitrogen, urea, and ammonia in blood testifies a sharp protein breakdown with decrease in detoxification and secretory functions of the liver and kidneys. The clinical picture of cancer intoxication is characterized by general weakness, increased fatigue, adinamiya, tachycardia, nausea and loss of appetite, pallor and an earthy shade of skin, perspiration, fever, muscle pains and headaches, sleep deprivation, anemia, muscular dystrophy, and body weight loss. At the same time there are signs of oxidative stress and disorders of lipid peroxidation with increasing levels of diene conjugates, Schiff bases, and other fractions of middle weight toxic compounds [5].

All these symptoms are indications for detoxification and apheresis therapy in oncological patients, mainly as preparation for the forthcoming operation. The detoxification is even more indicated

in case of mechanic jaundice due to compression of the bile ducts by the tumor. Such endogenous intoxication is even more aggravated during the surgery, which complicates the postoperative management [6]. Quite often inflammatory processes also emerge. Carrying out apheresis therapy before oncological operations promoted decrease in severity of an operational stress, reduction of medicinal support need, and postoperative complications incidence. Such procedures were also required in the postoperative period for elimination of the arising toxic-septic complications. After a lung cancer surgery the "the postoperative syndrome" may occur when the patient develops endotoxemia, activation of lipids peroxidation, and hypercoagulation postoperatively. Plasma exchange, hemosorption, intravenous laser irradiation of blood reduced the postoperative complications incidence and hospital lethality.

For more than 100 years there is a known association between tumor processes with tendency to produce thromboses in the peripheral vessels, which are manifested by migrating thrombophlebitides, thromboses of deep veins of the lower extremities and a small pelvis, thromboembolia of the pulmonary and peripheral arteries that occursin 15-45% of patients, and in the postoperative period – in 55% of them. These changes have systemic character and don't depend on the tumor type [7].

Development of DIC-syndrome signs with hemorrhages and consumption of coagulations factors and platelets is possible. Besides, some chemotherapeutic preparations (L-asparaginaza, mitomycin, cisplatin) are also connected with development of thrombotic complications. In particular, high doses of chemo preparations during marrow transplantation quite often lead to the liver veins occlusion damages. Tumor cells can make the coagulative cascade active, producing their procoagulant factors and stimulating prothrombotic properties of the blood cells [8].

Tumors also appear due tounfavorable environmental conditions – in addition to the known direct effects of tobacco smoke components, the presence of a wide variety of environmental carcinogens is also important. In particular, they found a relationship of increased content of heavy metal salts in the body, such as mercury, lead, aluminum, cobalt, lithium and copper and breast cancer. This has been the basis to develop preventive methods for this disease,using cascade plasmapheresis [9].

Development of tumors is closely connected with the immune defenses' condition. In case of immunodeficiency tumors develop in 100-1000 times more often than in general population. The immunosuppressive therapy, being vital for prevention of rejection reactions in transplantation, also promotes increase in tumors incidencein 4-100 times. The known cancerogenic effect of a number of chemical compounds, viruses, and penetrating radiation is in many respects connected with development of a secondary immunodeficiency [10].

One of the main factors is the reduced activity of the cellular immunity [11]. And a normal person constantly produces cells with a different antigenic structure. They are diagnosed and removed by cytotoxic and killer T-lymphocytes. But when the latter are unable to induce apoptosis of the present tumor cells there are conditions for their subsequent extensive growth and spread created.

And the tumor process itself contributes to immunosuppression, especially considering the development of concomitant endogenous cancer intoxication. In addition, surgery with inevitable stress contributes to immunosuppression within 2-4 weeks after it. In addition, all types of chemotherapy and radiation therapy also lead to secondary immunodeficiency – reduced number of T-lymphocytes, which are important in the tumor cells destruction.

The brightest illustration of it is the high incidence of malignant tumors in patients with AIDS, which is the one of the main causes of death. Tumors incidence in those who have undergone radiation therapy is also great. Tumor process promotes immunosuppression, especially considering the accompanying endogenous cancer intoxication developed. Besides, a surgery causing an inevitable stress, promotes immunosuppression within 2-4 weeks after it. Besides, all types of chemo- and radiation therapy also lead to a secondary immunodeficiency when the quantity of T-lymphocytes, which are important in destruction of tumor cells, decreases.

The strongest immunosuppressive effect of the radiation therapy is the direct damage of the lymphoid tissues and circulating lymphocytes. This effect remains not less than two years after the radiation. The majority of antineoplastic preparations also inhibit immune reactions. Some of them (6-mercaptopurin, cytosar, methotrexate in combination with leucovorin and 5-ftoruracyl) also suppress T-lymphocytes. Cyclophosphamide and phosphamide inhibit the cell-mediated immunity [12].

Radio-and chemotherapy and their complications

Nowadays, high-dose chemotherapy followed by marrow transplantation becomes more and more widely used. However, in such cases within 12-18 months a marked immunodeficiency picture develops, both of cellular and humoral, and 20% have weakness, depression, low working capacity, frequent recurrent catarrhal diseases after 18 months [13]. Even a weak virulent infection in such cases quite often leads to serious septic complications with severe endotoxemia that often cancels successful correction of the main disease with the subsequent tragic outcome. And in our practice time and again we managed to interrupt such fatal development of septic complications by means of hemosorption and the subsequent plasma exchange enabling to restore the system of immune protection.

Any exo- and endogenous antigens are to be captured by macrophages, and cytostatics reduce their quantity in the body, while the antigens activated by macrophages would have to promote transformation of T- and B-lymphocytes in immunoblasts, being predecessors of effector cells – T-killers and plasmatic cells, producers of antibodies.

All impacts on the body, which suppress proliferation (radiation, cytostatics, anti-metabolites), lead to reduction of the effector cells formation and weakening of T-killers function. It also causes suppression of the body ability to form the cellular and humoral mediated immune reactions.

The immune protection quality affects both system of malignized tumor cell recognition and its timely destruction. In the body during the continuous renewal of cell and other tissues structures some defective tissues develop, often with elements of malignant growth. The immune system has to distinguish and immediately destroy such cells with the changed antigen structure. Studying development dynamics of the transplanted tumors in animals proves that the immune system can distinguish and destroy 10^5-10^6 malignant

cells. Exceeding this quantity is fraught with immune exhaustion ("paralysis") resulting in progression and uncontrollable growth of a tumor. One third of the patients, having undergone radical operation, still have some amount of tumor cells, and considering the broken immunity the remained tumor cells can cause recurrence and metastases.

Vascular endothelial factor of growth may also be considered to play its role of angiogenesis main mediator, promoting neovascularization of solid tumors, without which their progressing growth would be impossible. Activation of this factor also promotes proliferative diabetic retinopathy, progression of rheumatoid arthritis and psoriasis. Monoclonal antibodies to this factor, suppressing angiogenesis, also promote delay of growth of solid tumors [14].

All this makes all the measures to restore the immune protection normal level in oncological patients to be extremely important, which directly affects the efficiency of the whole medical therapy complex and the patients' survival rate. Thus, of course, it is impossible to ignore well-known methods of specific and nonspecific immunotherapy, drug and mediated - usual bacterial vaccines (BCG, smallpox, etc.), polysaccharides (zimozan, pyrogenal, prodigiozan), and inductors of an endogenous interferon-formation. It is known that levamisole (decaris) and interferon increase survival of oncological patients.

However, radio- and chemotherapy lead not only to immunodeficiency. Consequences of chemotherapy are the accumulation of cytostatic preparations, being toxic not only for tumor cells, but also for other tissue structures [15]. Secondary metabolic disturbances, including leukopenia (<2,0x10^9/l), anemia (hemoglobin <60 g/l), and thrombocytopenia (<50x10^9/l), predispose to development of hemorrhagic and infectious complications with a complex of multiple organ failure. Besides, chemotherapy promotes disintegration of the tumor tissues elements (*metastases*), which remained after the operation, followed by accumulation of the degraded proteins, lipoproteins, oligopeptides, and leads to additional asthenization and a tumor cachexia.

When using different methods of radiation therapy, peroxides (peroxide of nonsaturated fatty acids), phenol, ketoaldehyde, oligopeptides of middle molecular weight, molecules with reactive free radicals also have its effect. This is especially dangerous in elderly patients, which often leads to discontinuation of chemotherapy [16]. In particular, Nivolumab, used in treatment of non-small-cell carcinomas of the lungs and melanoma, can cause severe myasthenia and myocarditis [17-19]. Cisplatin causes severe thrombocytopenia, hemolytic anemia with kidney damage [20].

Thus, in various organs such complications appear after different time. So, radiation burns of the skin occur practically right after the radiation, acute radiation pneumonitis – in 2 months, radiation pericarditis – in 6-9 months, radiation induced sarcomas – in 10-15 years. There is also a correlation between radio- and chemotherapy, carried out in childhood, with tumors of the brain and neurofibromatosis developing in adults [21]. There are also reports about other kinds of changes in the lungs, heart, gastrointestinal and urogenital tracts, and in bones [22,23]. Hemolytic anemia as a result of carboplatin and some other preparations administrations is described that also demands plasma exchange [24,25]. Fatal endogenous intoxication develops under the influence of cisplatin as well [26]. Anthracyclines and trastuzumab have high cardiotoxicity [27,28]. High-dose chemotherapy can lead to interstitial pneumonia followed by fatal respiratory distress syndrome [29]. After chemotherapy, neurological disorders such as encephalopathy, cerebellar syndrome, myelopathy, peripheral neuropathy are also possible [30]. It considerably complicates the patients' condition, interferes with timely repeated planned courses of chemotherapy.

Therapeutic apheresis in oncology

Tumors, especially malignant are certainly to be surgically removed and the subsequent radio- or chemotherapy to be performed, but apheresis therapy is also indicated to perform detoxification, facilitating the subsequent surgery and eliminating toxic consequences of radio- and chemotherapy.

One of the most powerful methods of immune correction and detoxification is apheresis therapy. The corner principle of the last consists in elimination of the initial causes, inducing immunodeficiency. Among them endotoxiemia plays the leading role and if this immune system burden left removed it is difficult to count on essential and long effect of the immunostimulant therapy. Plasmapheresis proves to be the most effective method of homeostasis normalization.

On the other hand, the immunostimulant effect of quantum photohemotherapy, which is ultra-violet and laser irradiation of blood, is well-known. However, the possibility to use photohemotherapy in oncological diseases is still being discussed, considering the known cancerogenic effect of ultra-violet radiation. Though, mechanisms of solar radiation impact on the skin is more thermal than ultra-violet (except for melanomas) and it should not be confused with ultraviolet rays radiation of a limited blood volume - to 2 ml/kg of body weight, creating an immune stimulation effect. Besides, there are a lot of reports about successful UV-radiation of blood in oncological patients in the postoperative period, generally to prevent and treat infectious complications.

Monochromatic laser radiation of blood has no less expressed immune stimulation effect, which is safer and deprived of many potential dangers. Infrared laser radiation of a tumor zone in experiment showed lack of its stimulating impact on the tumor growthrate. Laser radiation of blood (more than 6000 procedures) was used to treat precancer and chronic diseases of the stomach, to prevent and treat postoperative complications in lung cancer sufferers, to correct postoperative complications in patients with stomach cancer, to prevent and treat radiation therapy complications of the skin and mucous membrane in patients with tumors of the head and breast [31]. Reparative processes stimulation, anesthetic effect without signs of tumor and metastases growth stimulation is shown. Laser radiation reduced the frequency of early and late radiation damages of the normal tissues surrounding the tumor, which appeared in the zone of radiation therapy impact. Blood laser radiation promoted improvement of the blood rheological properties and microcirculation with decrease of postoperative complications in case of malignant tumors of the stomach and bowels [32].

Positive impact of the blood laser irradiation in oncological patients has been experimentally proved. Marked changes in the primary tumor structure are noted, up to death of the tumor cells, using intravascular radiation of the blood with low-intensive He-Ne-laser. Metastases in the irradiated animals had much smaller size and an

accurate form, than in the non-irradiated ones [33].

All this justifies indications for apheresis therapy in oncological patients not only as preparation for an operation or in emergency cases of pyoinflammatory complications after operations, but also in order to eliminate the radiation and chemotherapy negative consequences. In particular, serious consequences of gemsitabil and cyclosporine-A administration with development of not only thrombocytopenia, but also of thrombotic microangiopathy with multiple organs insufficiency are described [34,35]. Pembrolizumab promoted myasthenia aggravation [36,37]. Mitamycin C is also capable to cause thrombotic microangiopathy with serious damage of the kidneys [38]. And only by means of plasma exchange it was possible to eliminate such consequences and to continue further treatment of such patients [39-41]. Plasma exchange also helped to eliminate toxic consequences of cisplatin high doses [42-44]. With help of plasmapheresis it is possible to eliminate severe consequences of tumor cells lysis caused by chemotherapy [45]. Plasmapheresis helped to eliminate hemolytic-uremic syndrome with signs of thrombotic microangiopathy and acute kidney failure after high-dose chemotherapy [46,47]. Plasmapheresis is widely used for elimination of some other serious consequences of chemotherapy [48-55].

It was considered that plasma exchange, besides toxic substances removal, is capable to considerably improve the immunologic status and homeostasis in general including when carrying out anticarcinogenic immunomodulation [56].

Kiev research X-ray-radiological oncological institute has got the greatest experience of an extracorporeal detoxification and apheresis therapy that account for 700 procedures of hemosorptionin 621 patients when leukopenia and other consequences of chemo- and radiation therapy were mostly the indications to it [12]. The indications were marked intoxication (initial and obtained during beam- and chemotherapy), increased individual sensitivity to these methods or preparations, inhibition of blood producing organs with leukopenia, liver and kidneys dysfunctions, and overdoses. In the latter case or in "shock" doses hemosorption was carried out as soon as possible after the radiation or chemotherapy in combination with forced diuresis. Hemosorption in the first days after a shock dose of chemotherapy allowed avoiding severe leucopenia. Only thanks to intensive detoxification it was possible in some cases to conduct a full course of anticancer therapy.

Plasma exchange was successfully used in intensive therapy of a myelotoxic agranulocytosis in oncological patients and leukopenia in 24 patients with lymphogranulomatosis, having undergone intensive radiation therapy [57-59]. After plasma exchange with removal of 1500-2200 ml of plasma a distinct normalization of level of middle weight molecules, creatinine, urea, proteinaceous fractions was observed. The number of leukocytes in the course of radiation exposure decreased from 5.47 to $3.01x10^9$/l, but after plasma exchange it increased up to $4.62x10^9$/l and in a week it kept at the level of $4,46x10^9$/l.

Our own small experience to use plasma exchange in the course of radiation and chemotherapy in 25 patients with pancreatic cancer also is the evidence to it [60]. In this severe type of an oncological pathology, at which operability of a tumor doesn't exceed 50%, radiation and chemotherapy is often considered the only method of treatment. However, the serious initial background of endotoxemia, especially in case of non-resected tumors, was considerably aggravated by chemo- and radiation exposure that often made impossible to carry out a full course of such treatment.

In the beginning introduction of apheresis therapy methods was caused by increasing leukopenia threatening to interrupt a course of radiation therapy. After the first procedures of plasma exchange it was possible to restore the initial level of leukocytes and to continue the treatment. Further tactics consisted in preventive procedures of plasma exchange to prevent such complications. These procedures were carried out weekly within a month. Thus, complications still developed, but their rate and severity in the main and control groups significantly differed. The last group enrolled patients with pancreatic cancer comparable with the stage and severity of the patients from the main group, receiving only radiation and chemotherapy but without plasma exchange. Plasma exchange promoted the best tolerance of radiation and chemotherapy. The most frequent complications such as anorexia, nausea and vomiting were observed 3 times less often, and more serious conditions (stomatitis and enteritis) didn't develop at all. Toxic suppression of blood producing organs was lowered. Anemia, leuco- and thrombocytopenia developed 2-3 times less often. Carrying out plasma exchange made it possible not to interrupt the treatments due to the increasing endotoxemia (Table 1).

Table 1: Complications during radiation therapy for pancreatic cancer

Signs	Radiotherapy + Plasmapheresis (n = 22)	Radiotherapy only (n = 39)
Nausea / vomiting	4 (18%)	21 (54%)
Anorexia	–	10 (25%)
Diarrhea	–	5 (13%)
Loss of body weight	9 (41%)	34 (87%)
Anemia <95 g / l	–	6 (15%)
Leukopenia < 3 x 10^9 / l	–	13 (33%)
Thrombocytopenia < 100 x 10^9 / l	–	3 (8%)
Fever > 38 °C	–	3 (8%)
Blood transfusion	–	3 (8%)
Platelet transfusion	–	5 (13%)
Interrupting RT	–	4 (10%)

Positive effect of plasmapheresis was reported in 30 cancer patients receiving palliative course of radiation and chemotherapy [61]. On the background of improving the general condition and well-being, the level of substances of the average molecular weight and the leukocyte intoxication index decreased by 34% and 38%, respectively. More stable results were achieved with simultaneous enterosorption, laser irradiation of the blood and indirect electrochemical oxidation of the blood.

Indications for apheresis therapy in case of radiation therapy are doubtless for the antineoplastic effect of radiation occurs only during this process, and after the procedure the peroxide compounds

formed during its course have no more antineoplastic action, but they increase the general level of endotoxemia with appearance of a number of secondary toxic metabolites, damaging the healthy tissues as well. However, in chemotherapy there can be a danger of premature removal of antineoplastic chemo preparation that can cancel the effect of such treatment.

At the same time it is known that these types of therapy reach the greatest antineoplastic effect during introduction of chemo preparation; then their residual concentration is not so cancerocidal but it remains toxic for the normal tissues. Therefore, they are to be eliminated from the body, as well as the products of the excited secondary metabolic cascades, and, the main thing, the products of the tumor cells disintegration for the body isn't able to cope with such amount of toxic substances, which is actually a kind of self-poisoning. On the other hand, timely carrying out apheresis therapy will enable to considerably increase the efficiency of both surgical and chemotherapeutic treatment methods in oncology.

The pharmacokinetics of the majority of antineoplastic preparations is rather uniform and consists in achievement of the maximum concentration of preparations in blood at the moment and in the next few hours after their introduction. In 12 hours more than a half of their initial quantities are eliminated from the body [15,62]. Therefore two approaches can be quite justified: to carry out a procedure of plasma exchange already on the next day after the chemo preparations introduction and apheresis therapy after end of the full course of chemotherapy. In the first case procedures of plasma exchange can be performed on the stage of the preparations administration, in the second - carrying out a continuous course of a plasma exchange (3-4 procedures in 1-2 days). There are known effects of detoxification by means of enterosorbtion, in oncological patients as well [63-65].

Nowadays, liposomal forms of chemo preparations administration, in particular, of liposomal doxorubicine, are often used. The nanosizes of these preparations facilitate penetration into tumor tissues; however, elimination of liposomes by reticulo-endothelial system is complicated by polymers liposomes of polyethylene glycol that provides their accumulation in the body in 60 time'shigher concentration than that of doxorubicine [66]. To delete the residuals of doxorubicine liposomal fraction is considered beneficial by means of the most intense cascade plasma exchange in 48 hours after its administration [67-70]. Such nanoscale drugs can be perfectly removed by the usual plasmapheresis, and using cascade plasmapheresis can return them back.

In oncohematology a considerable homeostasis dysfunction develops after high-dose chemotherapy, causing almost full suppression of all marrow line ages when transplantation of marrow (stem cells) is carried out. However, in the background of such immunosuppression the risk of septic complications is very high. Thus, even the most powerful antibiotics aren't able to stop them, especially associated with developing multiple organ insufficiency. Only apheresis therapy can be of real help. Hemosorption is to be the first stage to capture the circulating microorganisms and to perform detoxification, and plasma exchange with replacement of the deleted plasma with fresh frozen donor plasma in volume to 1-1.5 CPV is to be the second stage. Only such tactics enabled us to improve patient's critical condition.

This observation can be an example of such case:

Dasha G., 2.5 years old, with the body weight of 12 kg, underwent treatment for an acute lymphatic leukemia in the R.M.Gorbachova Research Institute of Children's Hematology and Bone Marrow Transplantology in Saint-Petersburg. After the initial stage of chemotherapy for leukopenia she developed septic state with multiple organ insufficiency. From 14.02.09 she was on mechanical ventilation. From 17.02.09 having unstable hemodynamics a course of apheresis therapy was performed, namely, hemosorption on the Hemofenix device (JSC Trekpor Technology) with transmission of 1.5 l of blood through the VNIITU-1 column, 19.02.09 – membrane plasma exchange with removal of 500 ml of plasma (1.2 CPV) and its replacement with the equal volume of donor plasma; 25.02.09 – hemosorption and 26.02.09 – a final procedure of plasma exchange (400 ml) was started again. Stabilization of the patient's state was due to such intensive course of apheresis therapy, manifestations of respiratory distress syndrome, toxic encephalopathy and a renal failure were eliminated and the child was discharged from the hospital.

Attempts to stop rejection reactions after marrow transplantation using massive plasma exchange were rather effective, too.

To correct toxemic syndrome in malignant diseases of the blood system the first procedure of plasma exchange was combined with the beginning of chemotherapy or performed a day earlier [71]. The last procedure of plasma exchange finished the course of chemotherapy. And each next cycle of chemotherapy was carried out along with plasma exchange.

More than 20 years in graft-versus-host-disease (GVHD) the methods of extracorporeal photopheresis are used, though the mechanisms of its effects are still not quite clear [72-75]. Thus, the derived leukocytes are saturated with photosensitization preparation (psoralen) and are exposed to ultra-violet irradiation and then are returned to the patient [76]. Thus, the lost T-lymphocytes have to activate an anti-gene-presented cell [77,78]. This method is used both in T-cellular lymphoma and in transplantation of some organs (heart, lungs). Nevertheless, a disadvantage of this technique is the impossibility of simultaneous removal of the collected autoantibodies as well as other pathological metabolites that makes this procedure not fully effective. And besides, the course of such treatment can reach 20,000 Euros [79]. However, it has been shown that plasmapheresis used a day before each procedure of extracorporeal photo chemotherapy enabled to avoid GVHD [80]. And we are also convinced this tactics to be correct.

However there are also more significant indications for plasma exchange in oncological patients. They are based on the known fact that such patients have soluble circulating protein substances with molecular fraction of 70-150 thousand Dalton, inhibiting lymphocytes and macrophages killer activity and even promoting their apoptosis, which enables the tumor cells to survive in the body [81]. Thus, it is the tumor cells that are considered to be the producers of such inhibitors. One of the possible mechanisms of their action is inhibition of the of a tumor necrosis factor (TNFα) and other cytokines (IL-1, IL-6) cytolytic activity directed on the tumor cells destruction [82]. Thus, it appears obvious that using of these cytokine (TNFα) as a therapy even in high doses may not result in significant clinical effect and their totally toxic effect can be followed by additional complications.

It is due to it that the immunotherapy in patients with malignant tumors doesn't provide desirable results despite the progress in tumor growth control in cells cultures orin mice [83,84]. It is the circulating inhibitors that are most likely to limit the therapeutic effect of various antineoplastic vaccines and cytotoxic cells activated by various methods, namely of lymphocyte activated cells (LAC), etc.

Separation and an incubation of lymphocytes with a tumor-specific anti-gene (MUC1) were carried out followed by their introduction to the peritoneum cavity of patients with ovarian cancer of [85]. Besides, there were attempts of lymphocytes incubation with a thermo-shock protein of 70 (Hsp70) and IL-2 followed by their washing and intravenous administration back to the patients with colorectal cancer and non-small cells lung cancer [86,87].

However, it must be kept in mind that such cellular therapy is fraught with excitement of severe autoimmune reactions. So, there are reports about autoimmune diabetes, serious arthritis and myocarditis developed in such cases [88].

In such situation only plasma exchange appears pathogenetically justified. And indeed, such a concept was confirmed in experiences in 6 dogs with the induced tumors of the mammary glands and osteosarcoma. Cascade plasma exchange with removal of about 10 ml/kg of body weight plasma high-molecular fraction was used. After the first procedure hyperemia, local heat and a softening of the tumors were noted, after 2-3 procedures the biopsy showed focal hemorrhage, microthromboses and necrosis of the tumor tissues; and after five procedures the tumor regressed, residual tumor tissues were resected and within the next 1-4 years no recurrence of tumors it was noted until the natural death of these animals.

Such approach was also approved in clinical practice in 16 patients with different types of malignant tumors, in treatment of which all other standard methods of treatment were not effective. In total 12 such procedures within a month they underwent cascade plasma exchange 3 times a week in the volume of 5-25 ml/kg of body weight with adequate replacement of the patient's plasma high-molecular fraction with the similar fraction made by donor plasma cascade filtration. It resulted in marked clinical effect in 14 of these patients followed by disappearance of pains and the histologic study showed size reduction of the tumor and their metastases, and signs of the tumor cells necrosis. Thus, from these 16 patients in three of them there was the tumor tissues full lysis and necrosis, in six patients the tumors size decreased by 50% and more, in three patients the tumors reduction was below 50%, and in the other two patients there was only stabilization of the tumor process observed [89].

The earlier studies have also shown apheresis of such cellular immunity inhibitors to be effective in treatment of breast, kidneys, prostate, ovarian, bowel cancers, non-small cells lung cancer, sarcoma and osteogenic carcinoma, squamous cancer of the head, neck, lungs, cervical uterus cancer and direct correlation between decrease in the TNFR1 and TNFR2 level and extent of the tumor clinical regress have also been proved [90].

However, considering detection of such inhibitors not only in blood, but also in ascitic liquid and even in urine, it is possible to assume that cascade filtration does not completely remove them. Perhaps for this reason it was suggested to eliminate such exosomes of 30-100 nanometers in size by means of hemofiltration [91]. Besides, in low-molecular fractions of proteins and middle weight molecules there are quite a lot of toxic products, having accumulated in cancer patients, which are also to be removed from the body.

Therefore, one can consider that even a usual plasma exchange in half of CPV volume and in the same intensive mode of plasma replacement is able to provide the best removal of such inhibitors of antineoplastic protection natural mechanisms together with other components of endotoxemia and in combination with methods of surgical, chemical and radiation treatment it is able to provide more encouraging results of oncological patients treatment. Only these inhibitors removal can potentiate a more complete effect of cellular antineoplastic immunity stimulation. This hypothesis is also supported by other researchers [92].

Now, in our clinic we perform such a protocol of intensive apheresis therapy in oncological patients, consisting of up to 8 procedures of plasma exchange with removal of 0.5 CPV every time followed by donor plasma replacement in the ratio of 0.8:1 [93,94]. And only after 5-6 plasma exchange procedures we carry out incubation of lymphocytes allocated in the plasma exchange with interleukins (IL-1β - betaleukin 0.001 mg or IL-2 – roncoleukin 500 mg) in the thermostat within three hours with the subsequent return to the patients [94]. The received preliminary results (almost twofold increase in TNF-α, IL-2 and IFN-γ levels and increased life expectancy from 0.5 to 2-2.5 years) can be considered encouraging (Table 2).

Cytokines levels in oncology 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 the initial level are reliable (P<0.05)

It is notable that the IFN-γ level after plasma exchange decreased that is explained by its temporary actual washing away; however, after an additional course of plasmocyte apheresis with incubation of lymphocytes with cytokines there was observed its considerable increase. But increase of TNF-α and IL-2 levels occured red right after plasma exchange and it can be referred to the lymphocytes receptors unblocking after removal of inhibitors of their killer activity. It also proceeded after their incubation with cytokines.

The further step in this direction is to develop a technique of R-1 and R-2 proteins immunosorption for unblocking TNF-α used in patients with metastatic melanoma.

The restriction for apheresis therapy in oncological patients can be its rather high cost. However, alternative methods of cytotoxic effects correction can be even more expensive and more dangerous to health.

Conclusion

The presented findings clearly show both the worldwide increase in the tumor diseases incidence rate and the low efficiency of all the methods used for their treatment – from surgical, to radio-

and chemotherapy. At the same time, the tumor process itself is accompanied by intoxication, and the drugs used only aggravate it. Increasing endotoxicosis plays the leading role in than atogenesis. All this justifies the use of various methods of extracorporeal detoxification, both in preoperative and postoperative period, but mainly in support of radio - and chemotherapy.

Taking into account the immune disorders significant role both on the stage of emergence, formation and further progressive growth of tumors, there is an increased importance of extracorporeal immunotherapy methods aimed to remove the inhibitors of lymphocytes killer activity and excite their cytotoxic properties.

Such methods will also be justified in cases of radical excision of tumors in the absence of visible metastases. But it is almost impossible to guarantee the absence of tumor cells left in the surrounding or remote tissues. That is why in such cases extracorporeal immunotherapy methods are justified both to remove the remaining molecules inhibiting lymphocytes killer activity, and to restore their cytotoxic activity, which is to prevent the relapses.

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