PLASMAPHERESIS DURING RADIOTHERAPY OF PANCREATIC CANCER AND ITS POSSIBILITIES IN CANCER CHEMOTHERAPY.

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Abstract
Pancreatic cancer is among the most severe category of cancer, in which is not always possible radical surgery and hopes remain only on radiotherapy. However, this treatment is often accompanied by severe side effects, makes interrupt treatment. Using plasmapheresis can significantly reduce these negative impacts and ensure the safety of radiotherapy. There is also viewed the possibility of using plasmapheresis in cancer chemotherapy.

Key words: cancer, radiotherapy, chemotherapy, endotoxemia, plasmapheresis.

Introduction
In recent decades it has seen an increase in the incidence of pancreatic cancer (PCa). Since 1940, the incidence of PCa has increased by 4 times, reaching 11 per 100 thousand of population. In the U.S., PCa is the fourth leading cause of death from all cancers, taking more than 20 thousand persons a year. In Russia, the incidence of PCa in 1995 was 8.6 per 100 thousand of population, while in Moscow – 11.4. In pancreatic carcinoma it accounts for 10% of all tumors of the digestive tract [1].

Radical treatment is possible only in 10-15% of patients. Most patients (90%) die within a year after diagnosis. In 80-85% of cases diagnosed with PCa at a stage where there is already an outside pancreas spread of tumors, while 40% – distant metastases [1].

The problem of treating PCa is among the most complex issues of clinical oncology and abdominal surgery due to the nature and severity of the tumor surgery. Along with instant tumor spread to adjacent organs PCa often gives regional metastases, which are found in 40-50% of cases. Rich blood supply of the pancreas and tumor invasion of large vessels leads to frequent hematogenous metastasis. Long-term results of treatment of PCa, despite some tendency to improve, remain poor and life expectancy of patients after radical surgery is rarely more than 18 months. All these factors lead to the urgency of developing combined methods of treatment of this pathology.

Currently radiotherapy (RT) can be carried out with a particular effect in 50-80% of patients. The results of this treatment were significantly better than palliative surgery. The average life expectancy after combined treatment is 2.5 times higher than the average results of palliative surgery [1]. However, with the development of radiotherapy, improving treatment outcomes of cancer patients has acquired special urgency the problem of quality of life,
including in the process of treatment itself. Fundamental limitations to widespread use of radiotherapy in oncology practice are associated with side effects and complications (dysepsia, anemia, leukopenia, thrombocytopenia, etc.). Their frequency and severity increases proportionally with the dose of radiotherapy. These complications are associated not only with the consequences of the exposure, but also of the death of irradiated cancer cells. Therefore, it seems reasonable to use detoxification methods, among which the leading role belongs plasmapheresis (PA), when pathological products are eliminated from the body with the liquid part of blood – plasma.

**Data base information**

In the clinic of hospital surgery number 1 of I.P.Pavlov SPbGMU in the last 10 years radiotherapy for PCa was performed on 61 patients with apparatus "Agat-R" in the static mode by conventional fractionation (2 Gr), the combined total dose per week – 10 Gr, with 2-5 cross fields. The total estimated dose of treatment was 50-60 Gr.

In 7 patients, radiotherapy was preceded by surgical intervention, in others it is held after pancreateoduodenectomy (16), bili digestive anastomoses (18) and other activities (20). Before the start of radiotherapy for patients with Karnofsky status was not less than 60 points (mostly – 80-100), Hb – not less than 120 g/l, the white blood cells count – not less than 4.5 x 10⁹ /l and platelet count – at least 250 x 10⁹ /liter.

The course of radiotherapy applied membrane plasmapheresis on a portable device "Hemofenix" with plasma filter “Rosa” (Treckpore Technology Corp., Moscow) to remove about 30% of the circulating plasma volume (CPV) per session [Voinov V.A., 2010]. Compensation plasma removed conducted crystalloid, colloid and rarely only at lower protein content in the blood of less than 60 g/L after the treatment was poured 250-350 ml of fresh frozen donor plasma. PA course consisted of 3-4 sessions held weekly.

PA held on 22 patients. Men – 12, women – 10. Average age – 56 years (31-74). 5 patients had stage II-III cancer at 16 – IVA (without distant metastases). The control group consisted of 39 patients, which the PA was not performed. Men – 21, women – 18. Mean age 57.5 years (28-80). In 8 patients was II-III and 31 – IVA cancer stage.

**Results**

Major complications that arose during the radiotherapy of pancreas cancer are presented in Table. 1.
Table 1. Complications during radiation therapy for pancreatic cancer.

<table>
<thead>
<tr>
<th>Sign</th>
<th>Radiotherapy + Plasmapheresis (n = 22)</th>
<th>Radiotherapy (n = 39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea / vomiting</td>
<td>4 (18%)</td>
<td>21 (54%)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>_</td>
<td>10 (25%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>_</td>
<td>5 (13%)</td>
</tr>
<tr>
<td>Loss of body weight</td>
<td>9 (41%)</td>
<td>34 (87%)</td>
</tr>
<tr>
<td>Anaemia &lt; 95 g /l</td>
<td>_</td>
<td>6 (15%)</td>
</tr>
<tr>
<td>Leukopenia &lt; 3 x 10⁹ /l</td>
<td>_</td>
<td>13 (33%)</td>
</tr>
<tr>
<td>Thrombocytopenia &lt; 100 x 10⁹ /l</td>
<td>_</td>
<td>3 (8%)</td>
</tr>
<tr>
<td>Fever &gt; 38°C</td>
<td>_</td>
<td>3 (8%)</td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>_</td>
<td>3 (8%)</td>
</tr>
<tr>
<td>Platelet transfusion</td>
<td>_</td>
<td>5 (13%)</td>
</tr>
<tr>
<td>Interrupting RT</td>
<td>_</td>
<td>4 (10%)</td>
</tr>
</tbody>
</table>

As seen from the Table 1, the main frequency band of complications was significantly lower than the control. PA started to be carried out after the completion of the 5th session of RT (week course). During this period the patients begin dyspepsia, which significantly impair their quality of life. After PA half it was noted the improvement in health. In this group never had to interrupt the course of radiotherapy due to develop complications. There has never been leukopenia below 3 x 10⁹ /L, thrombocytopenia below 100 x 10⁹ /L, and anemia below 95 g/l. It was never required transfusion of platelets. In two observations noted leukocyte recovery and the level of hemoglobin that before PA decreased below the above levels at the beginning of radiotherapy.

In this group, nausea was short-lived (mostly immediately after the session RT), and cases of vomiting – isolated. Astheno-vegetative manifestations were also minimal. Poor appetite noted 70% of patients, but the true anorexia was not observed. 9 patients during radiotherapy of the lost weight by 3-5 kg (average 4.1 kg).

In the control group were nausea and vomiting in almost all patients, these symptoms increase during the first two weeks, when the irradiation was performed anteroposterior fields. Their intensity was greater than in the main group. It was prevailed vomiting II degree (60%). In 25% they had anorexia. 34 patients lost weight by 3-8 kg (average – 5.2 kg). There were diarrhea and fever (13% and 8%, respectively). Leukopenia occurred in 33% of patients, more rarely
thrombocytopenia and anemia. Accordingly there was a need for blood or platelets transfusion (2 to 4 doses). 4 patients developed complications due to radiation therapy had to be interrupted.

**Discussion**

Development of the tumor is accompanied by the accumulation of a number of pathological metabolites, which are largely the cause of patient asthenia, malnutrition and increasing cachexia. Cancer intoxication is a type of endogenous intoxication. Increase blood levels of non-protein nitrogen, urea, ammonia indicate sharp increase in protein destruction with a decrease detoxification and excretory functions of the liver and kidneys. The clinical picture of cancer intoxication is characterized by general weakness, fatigue, tachycardia, nausea and loss of appetite, pale and sallow complexion, sweating, fever, muscle pain and headaches, sleep disorders, anemia, muscular dystrophy, a fall of body weight [2].

All these phenomena determine the indications for detoxification and efferent therapy of cancer patients, mainly in preparation for the upcoming surgery. Detoxification more shows in the presence of jaundice in impaction of biliary tract tumor process. Often join also the inflammatory processes. A.V.Antonenko and V.N.Volkova [3] reported on efferent therapy before 222 cancer surgery, reducing the severity of operational stress, the need for medical support, the incidence of postoperative complications. Such procedures were required also in the postoperative period for the elimination of toxic arising septic complications..

In addition, the surgery itself and the inevitable stress contribute not only to endotoxemia, but immunosuppression for 2-4 weeks after it. In addition, all types of chemo- and radiotherapy induce as a result the secondary immunodeficiency – reduced number of T-lymphocytes, which are important in the destruction of tumor cells.

The most potent immunosuppressive property has radiation therapy, providing direct damaging effects on lymphoid tissue and circulating lymphocytes. This effect persisted for at least two years after irradiation. Most anticancer drugs also inhibit the immune response. Some of them (6-mercaptopurine, cytarabine, methotrexate and leucovorin combination with 5-fluorouracil) can also inhibit T-lymphocytes. Cell-mediated immunity oppressed also by cyclophosphan and phosphamide [2].

All effects on the body that inhibit proliferation (irradiation, cytotoxic agents, antimetabolites) lead to a reduction in the formation of effector cells and weaken the function of T-killers. This leads to inhibition of the body's own ability to form the cell-mediated and humoral immune responses.
One-third of patients who underwent radical surgery, remains in the body for a number of tumor cells, and in conditions of impaired immunity remaining tumor cells may be the cause of recurrence and metastasis.

All this makes us believe it is vital all measures to restore normal levels of immune protection in cancer patients, from which is determined the effectiveness of direct whole complex of treatment modalities and their life expectancy. Of course, one can not ignore the well-known methods of specific and nonspecific immunotherapy, medical and indirect – the usual bacterial vaccines (BCG, smallpox, pertussis, etc.), polysaccharides (zymosan, pirogenal, prodigiozan), inducers of endogenous interferon- genesis. It is known that levamisole (dekaris) and interferon enhance the survival of cancer patients.

But we can not forget one of the most powerful methods of detoxification and immune correction – an **efferent therapy**. Cornerstone of the latter is to eliminate the initial causes of immunodeficiency. Among them the leading role played by endotoxemia and without removing this press from the immune system it is difficult to expect a significant and lasting effect of immune-stimulate therapy. And the most effective method of normalization of homeostasis is **plasmapheresis** (PA).

Radiotherapy causes a change not only in tumor but also in the surrounding normal tissues. At the same time in various organs such complications are manifested through different times. Thus, radiation skin burns occur almost immediately after exposure, acute radiation pneumonitis – 2 months, radiation pericarditis – 6-9 months, radiation-induced sarcoma – in 10-15 years. Are also described and other changes in the lungs, heart, gastrointestinal and genitourinary tracts, bones [4, 5]. By using different methods for joining the irradiation exposure of peroxy compounds (peroxide of unsaturated fatty acids), phenol, ketoaldehyde, oligopeptides average molecular weight molecules and free radicals. This greatly complicates the condition of patients, prevents timely repetition subsequent planned courses of chemotherapy.

However, not only radiation but also chemotherapy leads the development of endotoxemia. Consequences of chemotherapy consist of accumulation of cytotoxic drugs, toxic not only to tumor cells, but also other tissue structures of the body [6, 7]. Secondary metabolic disorders, including – leukopenia (below 2,0x10^9 /L), anemia (hemoglobin below 60 g/l), thrombocytopenia (below 50x10^9/L) create the preconditions for the development of hemorrhagic and infectious complications with complex multiple organ disorders. Furthermore, chemotherapy facilitates destruction of the remaining after operation items of the tumor tissues (metastasis) which is accompanied by accumulation of degraded proteins, lipoproteins, oligopeptides, and leads to additional asthenia and tumor cachexia.
All this justifies the indications for efferent therapy in cancer patients, not only in training for surgery or when an inflammatory complications after surgery, but also to eliminate the negative effects of chemo-radiotherapy [8].

The greatest experience of extracorporeal detoxification and efferent therapy has been accumulated in the Kiev Research Radiological Cancer Institute – 700 procedures of hemosorption in 621 patients and testimony of their important place occupied by leukopenia and other effects of chemo- and radiotherapy [2]. Indications were as well as severe intoxication (initial and emerged during radiation and chemotherapy), increased individual sensitivity to these methods or drugs, inhibition of hemogenesis with leukopenia, liver damage and kidney, and overdoses. In the latter case, or "shock" doses, hemosorption performed as soon as possible after the treatment by radio- or chemotherapy combined with forced diuresis.

Hemosorption the first day after a loading dose chemotherapy allowed avoiding severe leukopenia and other complications. Only thanks to intensive detoxification it was succeeded in some cases, a full course of anti-tumor therapy [9].

PA has been used successfully in the intensive care myelotoxic agranulocytosis in patients with cancer [10, 11] and leukopenia in 24 patients Hodgkin's disease undergoing intensive radiotherapy [12]. After plasmapheresis with removal 1500-2200 ml of plasma was observed distinct clinical effect with the normalization level of middle weight molecules, creatinine, urea, protein fractions. The number of leukocytes in the process of radiation exposure was reduced from 5.47 to 3.01x10⁹ / l, but after PA rose to 4.62x10⁹ / l and a week later was maintained at 4.46x10⁹ / l.

S.V.Rudoy (13) also reported positive effects of PA in 30 cancer patients receiving palliative radiotherapy and chemotherapy courses. On the background of improving their overall health there was a 34% decreased level of an average molecular weight substances and 38% – leukocyte index of intoxication. More stable results were achieved by conducting parallel enterosorption, laser irradiation of blood and indirect electrochemical oxidation of blood.

Indications efferent therapy with radiation therapy may not cause doubt as antitumor effect of irradiation occurs only during this process, and after the session formed during its peroxide compounds antitumor effect no longer possess, but increase the overall level of endotoxemia with the advent of a number of secondary toxic metabolites damaging healthy tissue also. However, chemotherapy may be a risk of premature removal of anticancer drugs, which can negate the effect of such treatment.

At the same time it is known that the greatest antitumor effect of these therapies achieved during the course itself, after it is residual concentration of these chemotherapeutic agents are not so cancer-cidal but retain their toxicity to all other normal tissues. Therefore, they should be
discharged from the body, as well as products of secondary metabolic excited cascades and, most importantly, the destruction products of tumor cells, because the organism is not able to fight with this avalanche of toxic substances, almost – with self-poisoning. On the other hand, the timely holding of efferent therapy will significantly increase the effectiveness of both surgical and chemotherapeutic treatments in oncology.

The pharmacokinetics of most anticancer drugs is fairly homogeneous and is to achieve the maximum concentration of drug in the blood at the moment and the next few hours after their introduction. Already after 12 hours, more than half of the original amount of excreted [6, 14, 15, 16]. Therefore, it can be justified by two approaches: as a session of plasmapheresis on the next day after the administration of chemotherapy and an efferent therapy after completion of a full course of chemotherapy. In the first case PA sessions can be "attached" to the stages of drug administration, the second – to ensure continuous course of plasmapheresis (3-4 sessions every 1-2 days).

Currently, often are used liposomal forms of administration of chemotherapy, in relative frequency – liposomal doxorubicin. Nanosize facilitate penetration of these drugs in tumor tissues, but elimination of liposomes reticulo-endothelial system is complicated by the presence in their structure of liposomes polymers polyethylene, which ensures their accumulation in the body in an amount of 60 times greater than the concentration of doxorubicin [17]. Pütz G. et al. (18,19,20) and J. Eckes et al. (21) consider it appropriate to delete using complex cascade plasmapheresis remains of this liposomal doxorubicin fraction 48 hours after its introduction.

Confirmation of the above is also our own experience of using PA during radiotherapy in patients with pancreatic cancer. At this difficult form of cancer pathology, in which the interoperability of the tumor does not exceed 50%, radiation- and chemotherapy is often the only practicable method of treatment. However, heavy original background endotoxemia, especially when unremoved tumors significantly exacerbated chemo-radiation exposure, which often makes it impossible to conduct a full course of such treatment [22].

In our practice, PA was used initially in patients with cancer of the pancreas for detoxification during prolonged obstructive jaundice, which can significantly reduce the time of preoperative preparation. Then engaging methods of efferent therapy during radiotherapy was caused increasing leukopenia, threatened interruption of radiotherapy. After the first few sessions of PA able to restore the original level of leukocytes and continue treatment. In the future there described above preventive tactics of PA, without waiting for such complications [22].

Membrane PA was the most appropriate for this category of patients that before the course were already in a state of exhaustion and hypoproteinemia, making them more susceptible to
fluctuations in circulating blood volume. PA on a portable device "Hemofeniks" is the most "soft" method, which allows us to spend even in an unstable hemodynamics [23].

Known effects of detoxification also using enterosorption [24], including patients with cancer. It can be carried alone, but also be combined with the plasmapheresis.

However, there are even more significant indications for the use of plasmapheresis in patients with cancer. They are based on long been marked by the discovery, in such patients, circulating soluble protein substances with a relative molecular mass of 70-150 thousand Daltons, inhibitory killer activity of lymphocytes and macrophages, which allows tumor cells to survive in the body [25]. In this case it is considered that the tumor cells themselves are the producers of such inhibitors. One possible mechanism of action is the inhibition of the cytolytic activity of tumor necrosis factor (TNF-α) and other cytokines (IL1, IL6), aimed at the destruction of tumor cells [27, 28]. Thus it becomes apparent that, when used as therapeutic agents themselves of these cytokines (TNF-α), even at high doses, significant clinical effects can not be achieved and their general toxic effects may be accompanied by additional complications. Obviously, this is why, despite the success in controlling tumor growth in cell culture or in mice, immunotherapy in patients with malignant tumors does not provide the desired results [29, 30]. In all likelihood it is the presence of circulating inhibitors restricts the therapeutic effect of anticancer vaccines using various different methods and activated cytotoxic cells, particularly lymphokine-activated cells (LAK cells), etc.

This approach has been tested also in clinical practice in 16 patients with various types of malignancies, the treatment of which all remaining conventional treatments were not effective. Threaded plasmapheresis carried out them in a volume of 5-25 ml/kg body weight with appropriate substitution of a similar high molecular weight fraction of the plasma fraction produced cascade filtration when the plasma donation, 3 times a week in a total amount of up to 12 treatments per month. It is possible to achieve the clinical effect in 14 of these patients was accompanied by the disappearance of pain, reduction in size of tumors and their metastases, tumor necrosis signs histologically. For three patients reported complete lysis and necrosis of tumor tissue from six tumor size decreased by 50% or more, three tumor reduction was less than 50%, and the remaining two patients of the 16 patients had a tumor stabilization process [31].

Efficacy apheresis of cellular immunity inhibitors was confirmed in the treatment of breast, kidney, prostate, non-small cell lung cancer, ovarian cancer, colon cancer, osteogenic sarcoma and carcinoma, cancer of the head, neck, lung, cervix. It was shown a direct correlation between the decrease in the level of TNFR1 and TNFR2 and the degree of clinical tumor regression [32].
However, given the detection of inhibitors in the blood, not only, but also in the ascitic fluid and even in the urine, it can be assumed that the cascade filter is not completely removed them. Furthermore, low molecular weight protein fractions and secondary molecules are much toxic products that accumulate in cancer patients, and also require removal from the body.

Therefore, we can assume that a ordinary plasmapheresis at volume half CPV and in the same intensive mode plasma replacement able to provide a more complete removal of such inhibitors of natural mechanisms of antitumor protection together with other components of endotoxemia and in combination with the methods of surgical and chemo- radiation exposure to provide more encouraging results of cancer treatment. And only after the removal of these inhibitors can expect a more full effect stimulation of cellular anti-tumor immunity.

Such protocol intensive efferent therapy of cancer patients – up to 6 sessions of plasmapheresis with removal each time with 0.5 CPV replacement donor plasma in a ratio of 0.8 : 1 is fulfilled now in our department [9]. And only after 5-6 sessions we perform plasma exchange with incubating of isolated lymphocytes with IL-2 or IL-1β in the oven for three hours, then return patients [9]. The obtained preliminary results (almost twofold increase in levels of TNF-α, IL-2 and IFN-γ and the same increase in life expectancy) can be regarded as encouraging [33].

Known limitation of efferent therapy in cancer patients may be its relatively high cost. However, alternative methods for correcting the cytotoxic effects may be more costly. Thus, the rate of erythropoietin in cytotoxic anemia is to $12971 and for replacement transfusion $4481 [34]. But still do not know in what monetary units can measure the health status of the patient, the duration of its life or even the possibility of recovery.

References


