Original Research

# Controlled Eosinophilic Syndrome Against Cancer. Scientific Discovery and Practical Aspects of Immunotherapy

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## Abstract

Looking for a universal anticancer cure in the sphere of telomeres, stem and immunocompetent cells, eosinophilic peroxidase and telomerase inhibition, and apoptosis of 'immortal' cancer cells, the developers of Technology "Immunostimulation with the use of the controlled eosinophilic syndrome immunomodulator", scholars and doctors discovered natural defenses against cancer, developed and clinically tested means of metastasis blocking and tumor necrosis, which help to achieve long-lasting remission, and protect patients from possible cancer recurrence.

## Keywords

Immunotherapy – Cancer – Eosinophils – Telomerase – Cancer cells

## 1. Introduction

Of course, a dream to find a universal remedy and technology against all types of cancer, though being elusory at the moment, is very tempting. Why, even in the same circumstances, do some people develop cancer and others do not? We all have innate protection against cancer. Due to gene mutations, cancer cells can develop in any organism. For some reason immune system may miss the start of malignancies. However, only immunity is a key to

solving the problem of finding a universal anticancer drug. The main objective is to help immune system create a necessary and sufficient amount of immunocompetent cells – eosinophils – to kill the immortal cancer cells and teach the immune system to produce a sufficient number of such cells to resist cancer recurrence by creating Controlled Eosinophilic Syndrome against Cancer.

The significance of this phenomenon lies in the formation of a new interdisciplinary scientific basis, with the view to working out a universal concept of immunotherapy for a wide range of cancers. This discovery is a platform for further research, though at the moment it already has practical application in immunotherapy of various cancers with high efficacy.

# 2. The essence of scientific discovery

## 2.1 Objectives

The research objective is to find a universal means of fighting various types of cancer, using innate natural defenses at the cellular level.

## 2.2 Eosinophils: enemies or defenders?

Eosinophils, or eosinophil granulocyte leukocytes, were first described in the late XIXth century by Paul Ehrlich, but serious studies of eosinophils started only in the 1960s. Absolute eosinophile level in human peripheral blood ranges within 50-350 eosinophils/μl, or 3-5 eosinophils per 100 leukocyte series (up to 5%). Eosinophils are responsible for protecting the body from external pathogenic effects, as well as from internal threats – cellular mutations. The main functional elements of eosinophils are granules of toxic proteins and membrane receptors. The complex of toxic proteins released by degranulation of eosinophils defines positive and negative side effects of these cells on human homeostasis. There is a long list of various diseases starting with the word “eosinophilic ...”, when an increase in eosinophils causes destruction of healthy tissues. The team of scientists of Scientific Production System

"Fertility & Ecology", examining the influence of bioactive substances on the bone marrow, set the task of the safe use of toxic proteins of eosinophil peroxidase in anticancer activity.

## 2.3 Traditional and innovative mechanisms for cellular immunotherapy. New standards of quality at the crossroads of sciences

The discovery of telomeres (the Nobel Prize in Medicine 2009 [*1*]) made scientists think about immortal cancer cells and created motivation for telomerase inhibition. Scientists investigated the links between RNP enzyme telomerase and human cancer. Almost all major types of cancer were checked for the presence of telomerase activity. In most cases activity was detected [*2*]. The position of the telomeres (nucleoprotein structures at the ends of human chromosomes) is essential for the stability of chromosomes and the lifetime of the cell. Each time a cell divides, the ends of chromosomes are shortened, ultimately causing cell ageing and its apoptosis when telomeres become critically short. In contrast, cancer cells increase telomerase activity as they have the ability to divide infinitely and yet preserve their telomeres, thus causing cellular immortality. Recent studies in this area show that inhibition of telomerase eliminates these processes and can lead to a new anticancer strategy, which will significantly differ from conventional cytotoxic drug therapies [*3*]. The studies prove that strong inhibition of telomerase leads to rapid ageing of cancer cells [*4*]. Most tumor cells have high telomerase expression, unlike normal cells that express low or undetected levels of telomerase. Telomere shortening by means of telomerase inhibition leads to a marked reduction of cell division and apoptosis of cancer cells, and induces anticancer agents [*5–7*]. Eosinophils play a crucial role in this process: the studies established a strong correlation between eosinophilia and absence of telomerase activity; toxic eosinophil proteins inhibit telomerase [*8*].

Besides the role of eosinophils in telomerase inhibition, great attention of scientists is attached to eosinophils themselves: how toxic eosinophil proteins can combat cancer cells during degranulation. The studies established the relation between eosinophil concentrations and

survival rates after surgery, as well as the best conditions in tumor staging. Unlike eosinophils, relatively few lymphocytes can penetrate deep into the tumor, especially in fibrous stroma [*9*]. The studies proved that eosinophil peroxidase (EPO) can be found around and within the tumor (breast cancer) during degranulation of eosinophils, which is not the case with benign tissue images where eosinophil peroxidase is not detected [*10*].

Thus, the studies confirmed that eosinophils can penetrate deep into the stroma of cancer. Anticancer activity of eosinophils is related to their phagocytosis capacity and their cytotoxic effects on many types of cancer. In breast cancer, degranulation of eosinophils was detected in tumor tissue with the accumulation of toxic eosinophil proteins [*10*]. The impact of eosinophilic granulocytes on the intestinal gastric carcinoma cells led to the death of these cells, which was proved by degenerative changes of the tumor [*11*]. The studies of eosinophil infiltration of squamous cell carcinoma of the esophagus made it possible to include eosinophils into therapies against metastasis [*12*].

Many studies showed a correlation between elevated eosinophils and IgE level with antitumor effect. IgE, participating in eosinophil-dependent priming of tumor antigens, promotes the formation of long-term immunological memory [*13*].

During clinical trials of different types and stages of cancer we detected deficiency of eosinophils. There is an urgent need to activate bone marrow stem cells to develop the necessary and sufficient amount of these immunocompetent cells, which will eliminate malignant tumors. We set the task of the so-called shift to the left and increased the percentage of eosinophils in the total amount of white blood cells. Thus, we achieved an increase in the absolute level of eosinophils by several times without an increase in other types of leukocytes. Elevated eosinophils were successfully tested on various types of cancer with the view to eliminating solid tumors.

The developers of the controlled eosinophilic syndrome immunomodulator decided to use eosinophils as microphages with the view to radically eliminating malignant tumors in accordance with Technology "Immunostimulation with the use of the controlled eosinophilic syndrome immunomodulator" (hereinafter referred to as Technology of immunotherapy). To achieve this goal during immunotherapy the level of immunocompetent cells is drastically raised (10 times or more). Some scholars and experts may wonder whether it is safe. Eosinophil peroxidase and other eosinophil proteins are toxic to cancer cells, bacteria, helminths and protozoa. In combination with hydrogen peroxide, they affect mast cells and cause the release of histamine. In immediate hypersensitivity IgE and IgG antibodies react on the surface of mast cells, stimulating their degranulation and release of substances of anaphylaxis, histamine, prostaglandin D, eosinophilic chemotactic factor of anaphylaxis. Certain allergic reactions are possible at that stage. The substances of anaphylaxis are suppressed by eosinophils due to a whole set of enzymes. Phagocytosis of immune complexes containing IgE, and secretion of histamine inhibitor by eosinophils also reduce the allergic reaction. While using elevated eosinophils in immunotherapy we tested the processes described above, and dispelled our doubts. At the beginning of immunotherapy with the use of the controlled eosinophilic syndrome immunomodulator, when the level of eosinophils is still low, and IgE level exceeds reference values, 2.6% of the patients (less than 3 cases per 100 patients) developed a short-term allergic reaction of the skin which was easily removed orally with water. Subsequent controlled increase in eosinophils was accompanied by secretion of histamine inhibitor reducing an allergic reaction.

## 2.4 Conclusions

The search for universal technologies and drugs against cancer should be simultaneously carried out in the following fields: 1) inhibition of telomerase to eliminate cancer cells immortality and accelerate apoptosis of these cells; 2) the use of eosinophils for telomerase

inhibition; 3) the use of chemotaxis of eosinophils to penetrate deep into the tumor stroma; 4) the use of toxic eosinophil proteins to destroy cancer cells; 5) activation of hematopoiesis on the whole and shift to the left in order to maximize the production of eosinophils by stem cells of the bone marrow by reducing the percentage of other white blood cells, particularly lymphocytes and neutrophils, because their penetration power and efficacy in fight against cancer is not essential; 6) control of IgE level in eosinophil-dependent priming of tumor antigens; 7) creation of a protective barrier for healthy cells against possible affections by toxic eosinophil proteins, allergic reactions and anaphylaxis by means of inhibiting property of eosinophils, including inhibition of histamine, which can provoke oncological diseases.

In conclusion, I would like to summarize the steps vitally important to destroy malignant tumors, including metastasis. Firstly, it is necessary to cut the roots, the mere basis of cancer – to make cancer cells mortal and stimulate their apoptosis by inhibiting telomerase. Secondly, it is necessary to stop metastasis and accelerate tumor destruction, destroying only cancer cells and not affecting healthy ones (super-selective biochemotherapy by means of chemotaxis of eosinophils). These two problems can be solved in one step – raising the level of eosinophils. It is necessary to increase absolute value of eosinophils, making shift to the left, i.e. increasing the percentage of eosinophils by reducing the percentage of other white blood cells which do not affect cancer cells, leaving their absolute number under reference values. An increase in eosinophils is accompanied by a corresponding increase in IgE.

# 3. Technology of immunotherapy: Practical aspects

## 3.1 Materials and Methods

### 3.1.1 Basic material

The basic material is controlled eosinophilic syndrome immunomodulator, developed and produced by Scientific Production System “Fertility & Ecology”. The drug is used orally

according to Technology of immunotherapy. In 2009 the drug passed the federal examination and received a sanitary-epidemiological conclusion certificate.

### 3.1.2 Animal testing

Animal research of the drug, including toxicology and efficacy tests, was conducted in 1995 and still goes on in accordance with the requirements of the 3Rs (replacement, reduction, refinement), adopted in most countries [*14*]. Non-infected animals, developing cancer naturally during their life, are used for the experiments. It takes a lot of time to find a sick animal with the right diagnosis – cancer. From the ethical point of view, this approach is the most humane one, as the research outcomes include not only a scientific result (safe and effective dosage of the drug), but surviving animals. As a rule, medium and large breeds of dogs such as Chow Chow and Turkmen Wolfhound (Alabai) are used for the experiments.

### 3.1.3 Observational study

Research data have been collected by means of naturalistic observation of groups of people for 20 years as well as the treatment of people in the network of multidisciplinary clinics "Doctor Plus". As time goes by, the application area of the drug and Technology of immunotherapy involves new types of cancer. Research and current treatment are carried out in accordance with the Helsinki Declaration of 1975, and its amendments of 2000 and 2008. All patients are supposed to give their informed consent by signing the Contract.

### 3.1.4 Immunostimulation

Technology of immunotherapy uses natural, innate mechanisms to combat cancer. Natural defense against cancer is inherent in the human body. The cells of human body are constantly dividing and die in apoptosis – programmed cell death. About 50-70 billion of human cells die daily as a result of apoptosis. This replacement of lost cells is provided due to proliferation – the growth of cell populations by means of cell division [*15*]. Producing such complex objects as human cells on such a gigantic scale, certainly, there are situations when

some cells turn out to be defective. The most dangerous of them are cancer cells, the result of mutagenic processes. Unfortunately, each person has got them. Human immune system is constantly searching for these defective cells. P53 gene is responsible for it. In a healthy person, this gene activates generation of immunocompetent cells that destroy the enemy. The problem arises when there is deficiency of these cells, and at the same time there is an intense growth of cancer cells. If the number of killer cells produced is less in comparison to the intensity of the tumor growth, then intervention is required [*16*]. The main objectives are the following: 1) to make the immune system produce the missing part of immunocompetent cells – eosinophils – by stem cells of the bone marrow. Empirical studies show that credit balance (resultant deficiency) of these cells, depending on cancer stage, is several billion cells per liter of a patient's blood; 2) to teach a patient's immune system to elevate the amount of protective cells on its own, if necessary (fighting against cancer recurrence).

### 3.1.5 Stages of immunotherapy. Results

Technology of immunotherapy is aimed at eliminating the deficiency of eosinophils. It is carried out in three stages:

Stage 1. Activation of hematopoiesis, raising the number of leukocytes due to generation of the maximum possible number of eosinophils.

Stage 2. Keeping the necessary number of eosinophils, individual for each patient, until complete elimination of cancer, tumor necrosis and elimination of their decay products.

Stage 3. Supportive therapy according to an individual program of rehabilitation, when production of eosinophils is kept at the desired level, individual for each patient (remission).

**Stage 1** usually lasts for a month. During this time eosinophils reach their maximum level. It takes 1 course of the controlled eosinophilic syndrome immunomodulator for relatively healthy people (cancer-free) to boost their immune system. Within 10 days eosinophils achieve their maximum level. The prolonged effect remains up to 30 days from the start of

immunotherapy [*17*]. In our practice, maximum level of eosinophils reached 63% with absolute value of $5.796*10^9$/L. The patient's vital tonus was higher than usual, no allergic reactions were detected. However, it is much more difficult to raise this level for patients with cancer. Even after a few courses of the immunomodulator it remains low.

The duration of Stage 1 for various types of cancer may vary. In stage I breast cancer Stage 1 lasts for 28-30 days. A single course of the immunomodulator raises the level of eosinophils from 2% to 56%, in absolute values from 0.182 to 3.92 thousand/μl (21.5-fold increase). In stage IV breast cancer eosinophil level was raised from 1% to 21%, in absolute values from 0.086 to 1.365 thousand/μl (15.9-fold increase) after six courses of the drug, i.e. two months. Bladder and ureter cancers require 34 days to reach maximum of eosinophils. Fig. 1 [*18*] shows the growth of eosinophils in absolute values under the influence of immunotherapy.

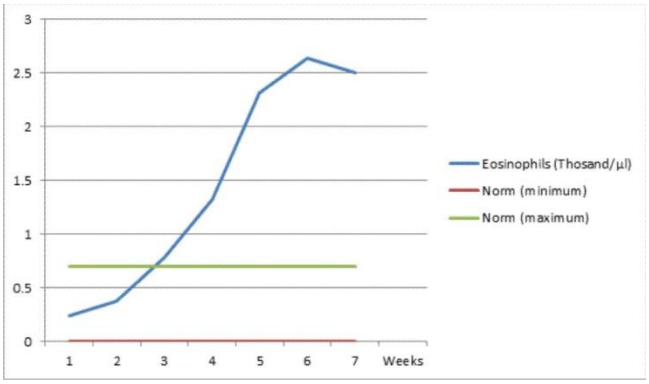


**Fig. 1**

Dynamics of eosinophils (thousand/μl) at Stage 1

Stomach cancer is more complex for immunotherapy even at early stages. The duration of Stage 1 for stage I stomach cancer is 2 months. The level of eosinophils was raised from 4.2% to 21%, in absolute values from 0.25 to 1.4 thousand/μl (5.6-fold increase). The duration of Stage 1 and the highest possible level of eosinophils are individual for each patient. They are determined by the potential for development of eosinophils by bone marrow stem cells (depending on the patient's age, time spent without immunotherapy, etc.). Telomerase inhibition takes place at Stage 1. Cancer cells lose their ability to divide endlessly without

changes in chromosomal endings. They become mortal again and live by the laws of apoptosis. Elevated levels of eosinophils significantly exceed reference values. Thus, the immune system is being trained to work in extreme situations, when the body needs extra reproduction of eosinophils, several times exceeding their usual number. The effect of controlling IgE level in eosinophil-dependent priming is based on implicit memory. This effect was tested in practice, when the patient's immune system on its own raised the level of eosinophils from 0.57 to 0.74 thousand/μl, i.e. above reference values.

**Stage 2** is aimed at eliminating the consequences of cancer (metastasis, tumors), as well as recovering affected organs due to regeneration stimulated by enzymes of the immunomodulator. Stage 2 may last several months (Fig. 2).

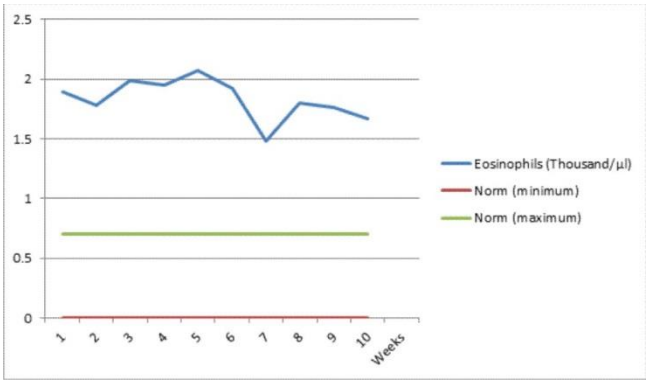


**Fig. 2**

Dynamics of eosinophils (thousand/μl) at Stage 2

This is the main stage, in which elevated eosinophils are used to destroy metastases, cancer cells and tumor stroma. Eosinophils are kept at the desired level by repeating courses of the immunomodulator up to 10 times.

The required duration of Stage 2 is determined individually for each patient. For instance, in stage IV ureter cancer and stage I bladder cancer (the same patient) the duration is determined by: 1) dynamics of tumor marker fall showing the decline of cancer activity, such as UBC (urinary bladder cancer) from 72.8 to 14.8 mcg/L (Fig. 3);

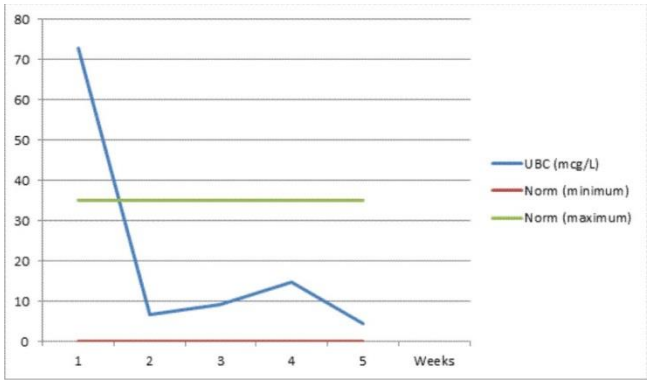


**Fig. 3**

Dynamics of UBC (Urine Bladder Cancer Antigen)

2) albuminuria caused by the decay of ureteral tumor from 27 October 2014 until 23 January 2015 (Fig. 4);

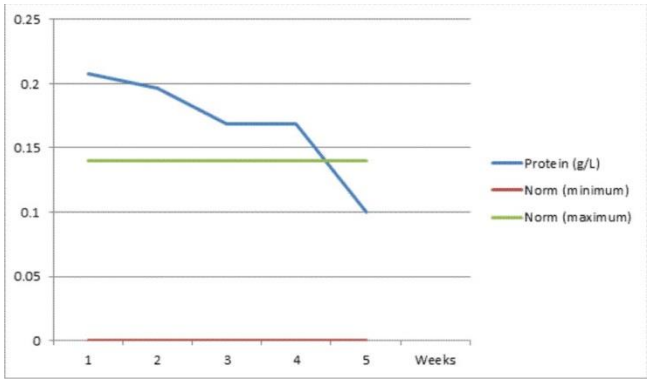


**Fig. 4**

Dynamics of albuminuria

3) decay products in the urine – whitish fibres caused by ureteral tumor disintegration and dark red pieces of blood vessels of the tumor stroma (Fig. 5);

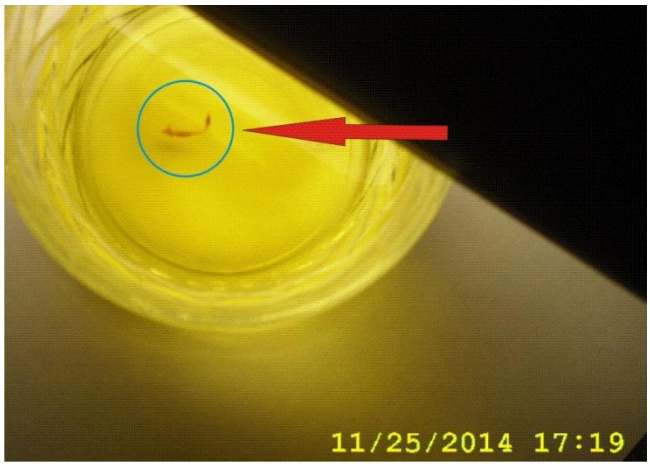


**Fig. 5**

A piece of stroma blood vessel in urine

4) dynamics of ferritin and homocysteine (a know-how, which is transferred together with a license to use Technology of immunotherapy). These mechanisms are universal for different

types and stages of cancer; 5) dynamics of ultrasound, MRI, etc. For example, Fig. 6 shows the dynamics of bladder ultrasound in stage IV bladder and ureter cancer (Fig. 6).

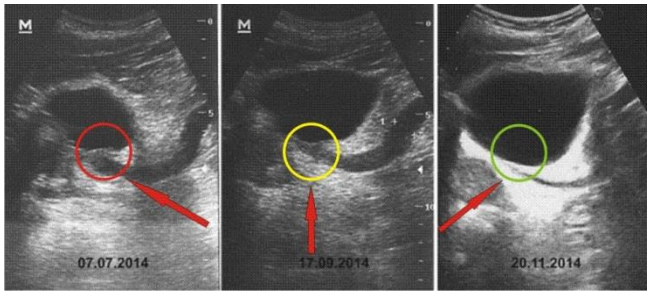


**Fig. 6**

Dynamics of ultrasound in stage IV cancer during immunotherapy

On the first image of Fig. 6 (07.07.2014) left ureter is dilated throughout from 3 to 11 mm, and there is a 14x9 mm neoplasm in urethral orifice which causes almost complete stenosis of the ureter. The diagnosis of the Moscow Oncology Research Institute is multiple primary synchronous cancer: 1. Stage I bladder cancer, T1NxM0, status post transurethral resection of 8 intravesical doses of doxorubicine. 2. Stage IV left ureter cancer, T4NxM0. Severe disorders of excretory function of the left kidney. The patient was supposed to undergo left nefrureter-ectomia with a resection of the bladder and paraaortic lymphadenectomy. The patient refused to undergo surgery in favor of the controlled eosinophilic syndrome immunomodulator (discharge summary from 08.08.2014). During immunotherapy, MRI was conducted on 10.07.2014 and 22.09.2014, which showed increase in the size of the neoplasm and dilatation of left ureter up to 13 mm. The second image of Fig. 6 shows the results of ultrasound from 17.09.2014 – dynamics is confirmed. Ultrasound on the third image of Fig. 6 (end of Stage 2 of immunotherapy) shows improvement. The ureter was reduced to norm (3 mm). Ureteral activity is intense. The function of the left kidney is restored. The patient returned to normal activities. During immunotherapy without surgery and chemotherapy we achieved tumor necrosis and elimination of its decay products (Fig. 4, 5), restoration of the affected organs – kidneys, ureter, urinary bladder.

**Stage 3** of immunotherapy is aimed at achieving long-lasting remission without cancer recurrence. It is analogous to chemotherapy. However, unlike chemotherapy, immunotherapy

has a clear target. Immunocompetent cells – eosinophils – receive chemotaxis signals and do the final “cleanup”, removing all effects of cancer. Moreover, the level of intoxication is determined only by the number of destroyed cancer cells, healthy cells are not affected. Stage 3 usually lasts for a year.

## 3.2 Statistical Analysis

To prove that the effect of the drug on the change in the level of eosinophils in the blood of patients is statistically significant, we used Student’s paired t-test. There are two sets of data with a normal distribution of the changes for 15 patients (sample size) before and after treatment (Table 1). The sample consists of patients aged 8 to 68, 70% of which are cancer patients, 30% are patients who want to boost immunity (chronic fatigue syndrome, etc).

**Table 1**

Eosinophils of patients before and after treatment

| Patient | Eosinophils (thousand/μl) | | Difference, d |
|---|---|---|---|
| | Before treatment | After treatment | |
| 1 | 0.2 | 4.99 | 4.79 |
| 2 | 0.14 | 0.86 | 0.72 |
| 3 | 0.08 | 0.33 | 0.25 |
| 4 | 0.1 | 1.43 | 1.33 |
| 5 | 0.25 | 1.4 | 1.15 |
| 6 | 0.48 | 0.91 | 0.43 |
| 7 | 0.36 | 0.73 | 0.37 |
| 8 | 0.24 | 2.64 | 2.4 |
| 9 | 0.34 | 1.47 | 1.13 |
| 10 | 0.15 | 3.17 | 3.02 |
| 11 | 0.15 | 0.81 | 0.66 |
| 12 | 0.13 | 1.87 | 1.74 |
| 13 | 0.18 | 4.92 | 4.74 |
| 14 | 0.09 | 1.36 | 1.27 |
| 15 | 0.1 | 5.8 | 5.7 |

The mean difference in eosinophils, according to Table 1:

$$\bar{d} = \frac{\sum d}{n} = 29{,}7:15 = 1{,}98 \quad (1)$$

Standard deviation of the differences in eosinophils:

$$S_d = \sqrt{\frac{\sum\left(d-\bar{d}\right)^2}{n-1}} = 1{,}78 \quad (2)$$

Standard error of the mean difference:

$$S_{\bar{d}} = \frac{S_d}{\sqrt{n}} = 0{,}46 \quad (3)$$

Student's paired t-test:

$$t = \frac{\bar{d}}{S_{\bar{d}}} = 1{,}98{:}0{,}46 = 4{,}3 \quad (4)$$

The degrees of freedom:

$$\nu = n - l = 15 - 1 = 14 \quad (5)$$

On $\nu = 14$ we have $t = 4.140$, which gives $p<0.001$. The calculated t-value is above the threshold. Therefore, there is strong evidence that the differences in eosinophils before and after treatment are statistically significant.

# 4. Discussion

## 4.1 Quality of Life

During immunotherapy, patients were cured from metastasis and solid tumors without undergoing surgery and physical and emotional suffering which it is usually accompanied with. Immunotherapy was used in breast cancer, stomach cancer, ureter and bladder cancer, thyroid cancer. Bone marrow transplantation was replaced by activating the patients' own bone marrow.

## 4.2 Survival rates

As Technology of immunotherapy is being mastered, survival rates have been improving. At present, patients with stage I breast cancer live more than 15 years. We managed to improve survival rate from 3 to 8-12 months for a patient with terminal advanced cancer (bedridden

patient), when we only started to implement Technology of immunotherapy. Nowadays Technology of immunotherapy allows to increase survival indefinitely.

### 4.3 Anesthesia

With stage IV cancer (very late diagnosis in advanced cancer) it is a matter of quality of life, or rather end-of-life issues. Analgesics often fail to help. They can partly dull the pain. Narcotics in this situation put patients into an altered state of awareness, where there is a gap between the true state of the body and its perception by the patient. The result, unfortunately, is the same – pain returns and gets more and more intolerable. What can Technology of immunotherapy do in such a situation? Rapidly growing cancer cells have a growing impact on the nerve endings, causing increasing pain. It is possible to stop this process by reducing frequency of cell division. Technology of immunotherapy allows to raise the level of immunocompetent cells that destroy cancer cells and tumor stroma. Thus, tumor activity is reduced, pain stops, there is no need in analgesics any longer.

### 4.4 Treatment of inoperable patients

Many patients for various reasons are deprived of medical care, most often when it is too late to do surgery to remove the tumor, because metastases affected most of the body. These patients are given a chance to fight cancer and win, provided that immune potential of stem cells outweighs cancer activity.

### 4.5 Cancer Prevention

After a preventive course of the controlled eosinophilic syndrome immunomodulator immunological memory makes the body produce a sufficient number of eosinophils on its own in case of cancer activity.

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# 6. Acknowledgments

The author is grateful for their assistance in the research to:

- N.A. Zabrodin, Chief Sanitary Inspector of the Udmurt Republic, Doctor of Medical Sciences, Professor;

- E. Berezikov, Doctor of Medical Sciences, Professor of European Research Institute for the Biology of Ageing;

- N.A. Kiryanov, Doctor of Medical Sciences, Professor, Vice Rector of Izhevsk State Medical Academy;

- O.V. Ostanina, Head of Medical Research Laboratory of Scientific Production System "Fertility & Ecology";

- E.I. Tytskaya, chief doctor of the network of multidisciplinary clinics "Doctor Plus".