Neoadjuvant Interferon in the Treatment of Melanoma Regional Lymph Node Metastasis

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Summary. The question about effective treatment of melanoma lymph node metastasis remains opened. The surgery is a single radical method that can delay further progression of the disease at this stage. However, the long-term results surgical operations are unsatisfactory. In practical oncology adjuvant interferon is widely used to improve outcomes of regional lymph node dissections. This addition significantly influences on disease-free survival and has a little impact on overall survival. These results motivate conducting researches on the application of combined regimes of interferon therapy. In the present study two-component scheme of interferon therapy (neoadjuvant and adjuvant) is evaluated. The patients with resectable metastatic melanoma in regional lymph nodes were included in this study. Prior to treatment patients were randomized into two groups: the first of them (study group) obtained induction course of interferon-α2b therapy before operation and maintenance course after surgery; the second (control group) began treatment with regional lymph node dissection with following adjuvant interferon-α2b therapy (induction and maintenance course). The toxicity and parameters of peripheral blood leukograms were studied during the treatment in both groups. The benefit in 2-year overall and disease-free survival was not registered in the any of the application schemes.

Key words: skin melanoma, interferon.

Introduction

Progression of skin melanoma generally begins from the clinical manifestation of lymph node metastases. The appearance of haematogenous secondary deposits without affected regional lymph nodes is a relatively rare phenomenon ranging from 8 to 10 % of cases [1]. In Ukraine one of the five patients (19.5%) which firstly have applied to the oncologist due to skin melanoma has already has a clinical sign of

metastasis in lymph nodes [2]. Among patients with primary melanoma in 20% of cases micrometastases in regional lymph nodes are detected [3].

Results of the surgical treatment of patients with clinical lymph node melanoma metastases are very modest. According to the literature data 5-year overall survival of patients after surgery is ranging from 59.0% to 24.0% depends on the volume of lymph node involvement [4]. Naturally, such statistic motivates to search techniques that can improve long-term results of surgical operations.

Nowadays, the interferon, which is used for over 30 years, is only proven effective agent that prevents the melanoma progression. In 2010 a meta-analysis of randomized studies of interferon alpha adjuvant therapy in patients with high risk melanoma was published. It has included data about treatment of 8122 patients. The authors concluded that the adjuvant interferon therapy reduces the risk of disease progression ($p < 0.001$) and improved overall survival ($p = 0.002$) [5]. Search of the best schemes, doses and regimes of interferon using in melanoma patients are extending continuously. One of the recent successful studies have focused on the pegylated interferon administration. A retrospective statistical analysis has shown significant benefit on disease-free survival in the study group. With 3.8 years median follow-up the disease-free progressive survival in the treatment group was 18% better compared with the observation group ($p = 0.01$). Another interesting fact has been found after more detailed analysis of the results EORTC protocol 18991: in patients with ulcerated melanoma pegintron significantly increased both overall and disease-free survival [6]. Pegilated interferon alfa-2b was approved by FDA in the March 2011 for adjuvant treatment of melanoma patients with metastases to redional lymph nodes after surgery (III stage).

A two-step scheme of interferon administration (pre- and postoperative) is relatively interesting option for patients with metastatic melanoma in regional lymph nodes. The results of such study were published in 2006. The authors have reported about positive results using this algorithm with high-dose interferon [6]. In our study the treatment scheme in patients with melanoma metastases in regional lymph node included neoadjuvant therapy with intermediate doses of interferon and following after surgery low-dose adjuvant interferon therapy.

Subjects and methods

41 patients with melanoma metastasis in regional lymph nodes were included in the study. There were following inclusion criteria: pathology proven diagnosis of skin melanoma, the presence of metastases in lymph nodes, absent metastases of other organs and tissues, the possibility of radical surgery, the satisfyng patient's condition (ECOG - 0 or 1). After examination (brain, chest and abdomen CT scanning, ultrasound of lymph nodes to identify their number and size) patients were randomized to the study and control groups.

The study group (n = 20) started their treatment with neoadjuvant recombinant α2b - interferon therapy. The drug was administered subcutaneously at a dose of 9 million IU once daily for 22 days (induction therapy). After 3 weeks of treatment result was evaluated with control ultrasound of regional lymph nodes and surgical treatment was performed. It consisted from regional lymph node dissection and wide excision of the primary skin tumor in cases when it was present. When diagnosis was pathology confirmed (on days 6-9 after surgery) third final stage of treatment was performed. It included adjuvant low-dose interferon therapy (3 million IU subcutaneously three times a week for 12 months).

The control group (n = 21) started treatment with surgery with following by the day 6-9 two-component scheme of interferon therapy - 9 million IU of recombinant α-2β - interferon once a day for 22 days (induction therapy) and then maintenance therapy with low-dose interferon (3 million IU subcutaneously three times a week for 12 months). Algorithm of treatment study group and control group is shown on Fig. 1.

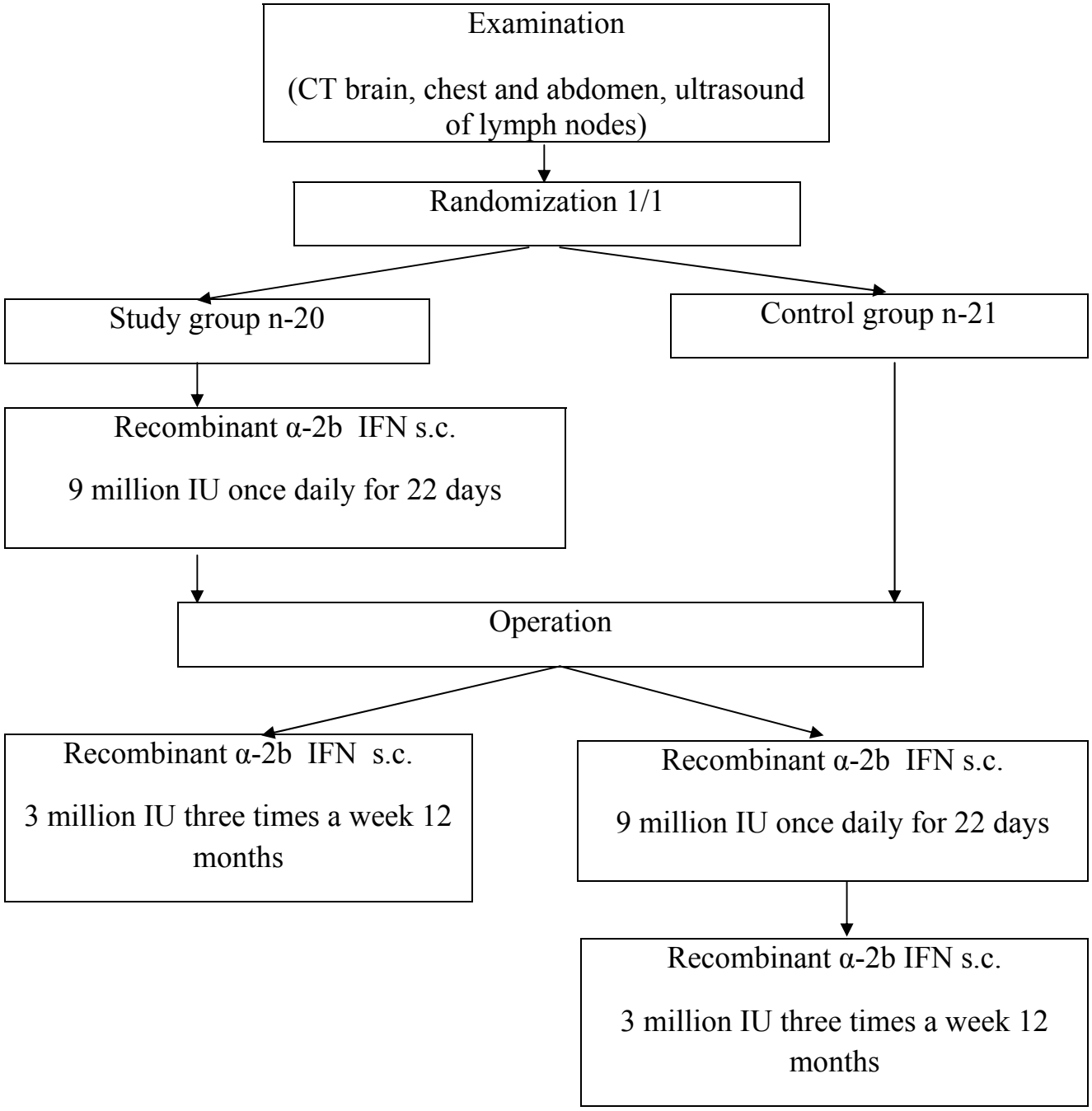
Examination
(CT brain, chest and abdomen, ultrasound of lymph nodes)
Randomization 1/1
Study group n-20
Control group n-21
Recombinant α-2b IFN s.c.
9 million IU once daily for 22 days
Operation
Recombinant α-2b IFN s.c.
3 million IU three times a week 12 months
Recombinant α-2b IFN s.c.
9 million IU once daily for 22 days
Recombinant α-2b IFN s.c.
3 million IU three times a week 12 months

Figure 1. Algorithm of treatment patients with metastatic melanoma in regional lymph nodes.

By the time of study enrollment the primary tumor was available in 1 patient (5.0%) in study group (the remaining patients had nodal metastases that developed at differrent time after removing primary tumor). In the control group the primary tumor was present in 2 patients (9.5%).

In the study group 13 (65.0%) patients had metastases detected in the ilio-inguinal regions and 7 (35.0%) patients had metastasis in the axillary. In the control group 11 patients (52.4%) had affected ilio-inguinal lymph collector and 10 patients (47.6%) had axillary lymph collector.

The study group included 20 patients aged from 24 to 70 years old. The average age of patients was 49.6 ± 2.01 years. Men accounted for 35.0% of the group (7 patients), women - 65.0% (13 patients).

The control group included 21 patients with an average age of 50.1 ± 3.4 years and ranged from 24 to 69 years old. The vast majority of the group were women - 57.1% (12 patients), the proportion of men was lower - 42.9% (9 patients).

Early and late results of treatment were evaluated. In the study group the directly impact of neoadjuvant therapy on the lymph node metastasis was searched. The changes in population composition of peripheral blood lymphocytes during the treatment were traced in both groups. For comparative analysis the disease-free and overall survival were studied and compared in both groups.

Statistical analysis of the data carried out using the programs Excel (MS Office 2003, XP) and STATISTICA 6,0 (StatSoft Inc., USA). The survival rate was estimated by Kaplan-Meier. Differences were evaluated as significant when $p < 0.05$.

Results and discussion

So 41 melanoma patients with regional metastasis treated in clinic in 2010 - 2011.

Typical for interferon adverse events were observed in both groups: flu-like syndrom (fever, chills, headache and myalgia), local erythematous reactions and fatigue. The most common complication was pyrexia, which occurred 2-3 hours after drug administration and in the most cases disappeared or reduced to subfebrile figures during 2 weeks of treatment. In the study group pyrexia grade I was present in 11 patients (55.5%), grade II - in 9 (45.0%) patients. In the control group pyrexia grade I was observed in 10 patients (47.6%), grade II in 10 (47.6%) patients, and grade III in 1 patient (4.8%). Pyrexia grade II-III required using anti-inflammatory therapy with non-steroidal anti-inflammatory drugs.

Dynamics of changes in peripheral blood leukocytes during treatment are presented in Tables 1 and 2.

During the research a patient's baseline in the control and the study groups a significant decrease of the total number of circulating lymphocytes compared with healthy donors was showed. The absolute numbers of the other types of leukocytes were within the physiological range. As a result, in the patient's leucocyte count the ratio of formed elements changed: percentage of lymphocytes decreased and the ratio of neutrophils increased.

In the control group in day 8-10 after surgery, the total number of peripheral blood lymphocytes increased to the level of healthy donors, the absolute number of other forms of leukocytes did not change significantly.

After induction course of interferon therapy that was performed in the control group as adjuvant treatment the content of white blood cells in peripheral blood changed significantly. It's changed by reducing the number of segmented neutrophils and lymphocytes ($p < 0.05$) compared with postoperative level.

Using maintaince course of interferon therapy during 3 months in the control group helped to restore the total number of white cell count in peripheral blood, particulary neutrophilic granulocytes, to the level of healthy donors. However, lymphocytopenia remained; there was a shift to the left leukocyte counts by increasing the number of banded neutrophils.

After the interferon therapy was finished all tested hematological parameters in patients of the control group were within the physiological values.

During the research of interferon impact on hematological parameters in study group following was revealed.

After induction course of interferon therapy that was conducted in neoadjuvant regime the content of white blood cells in peripheral blood reduced significantly compared with healthy donors. The absolute numbers of granulocytes were less than baseline but the count of lymphocytes slightly increased. Therefore, ratios of different forms of leucocytes changed leucocyte count: the percentage of neutrophils reduced significantly and count of lymphocytes increased compared with baseline.

It should be noted that such changes in leukogram after induction therapy were observed in the control group too.

At the day 8-10 after surgery in the study group a quantity of white blood cells and their forms in peripheral blood recovered. At this stage segmented neutrophils were particularly sensitive; their absolute number increased significantly that may be caused by the features of post-operative period.

During the maintenance course of the postoperative interferon therapy (3 months) in the study group leukocytiopenia developed as a result of decreasing number of segmented neutrophils and lymphocytes. At the same time leukocyte left shift was fixed by increasing the number of stab neutrophils, as well as in the control group at the same period. A significant increase of the relative content of monocytes was observed in the study group compared with the control group.

It’s found that when maintenance course of interferon therapy finished lymphocytopenia in the study group remained. Other hematological parameters were within the physiological values.

Thus, we can conclude the following. The both treatment regimens tolerated quite well, don’t lead to significant complications and don’t worse the disease. When we assesed clinical results firstly it was noted that the partial regression of affected lymph nodes was observed in the study group after neoadjuvant interferon therapy. It was observed in two patients that accounted for 10 %.

At 2 years follow-up in 5 (25.0%) patients of the study group developed further disease progression, 3 (15.0%) of them died. In the control group progression occurred in 7 (33.3%) patients and 3 (14.3%) of them died.

Curves of overall and disease-free survival are shown in Figures 2 and 3. So, the 2-year disease-free survival in the study group was 75.0 ± 9.2%, in the control group was 67.1 ± 10.2% (p> 0.05). 2-year overall survival in the study group was 85.1 ± 7.9%, in the control group this figure was 85.7 ± 7.6%.

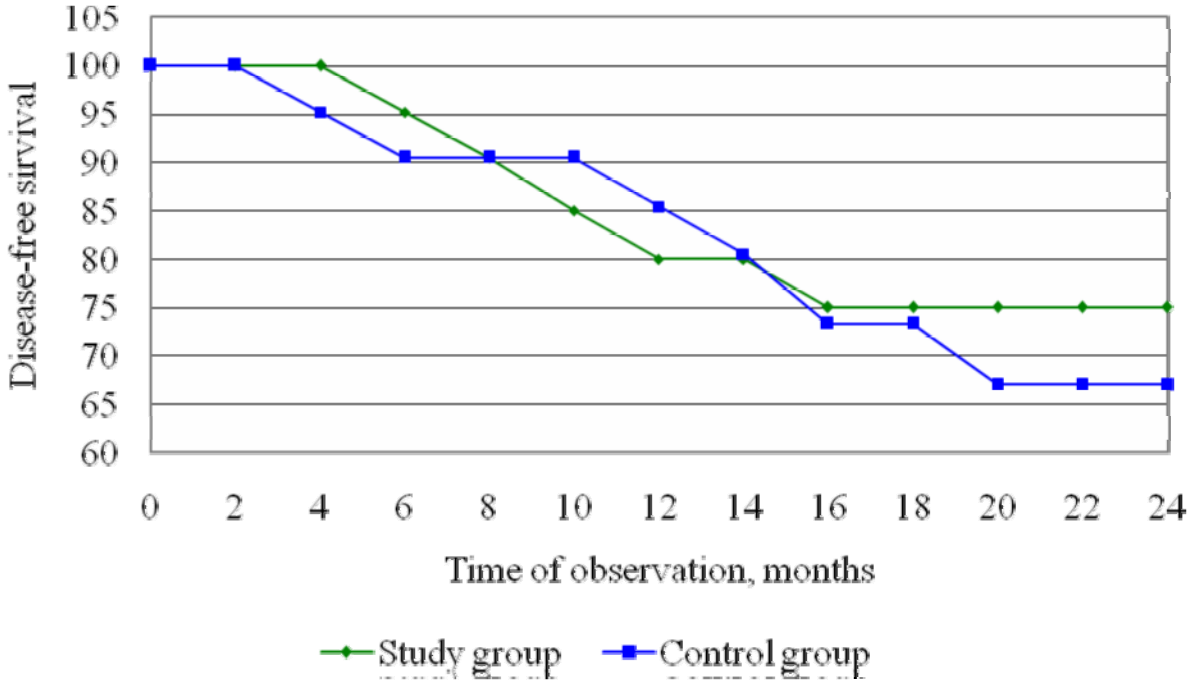

Figure 2. Two-year disease-free survival

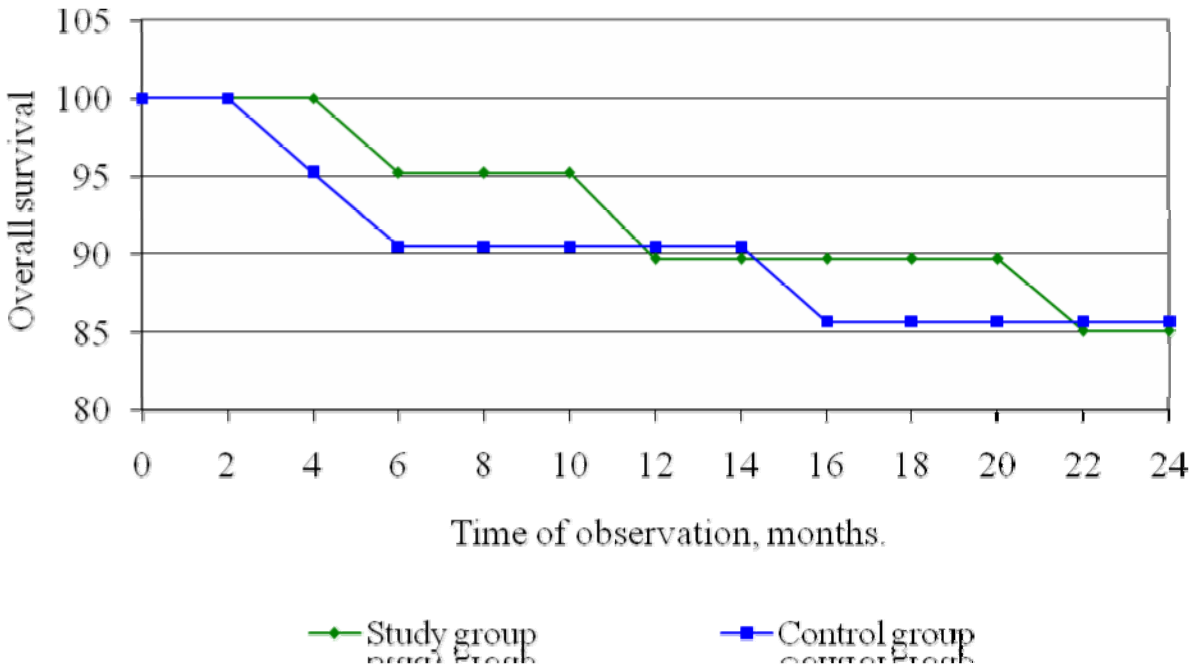

Figure 3. Two-year overall survival

Conclusions

1. Neoadjuvant regim of interferon therapy was well tolerated and wasn't associated with severe toxicities.

2. Preoperative interferon therapy can cause partial regression of melanoma metastasis in regional lymph nodes.

3. The proposed method of neoadjuvant interferon therapy resulted in a nonsignificantly tend to improve 2-year desease-free survival in patients with melanoma metastasis in regional lymph nodes (2-year desease-free survival was 75.0 ± 9.2 % in the study group and 67.1 ± 10.2 % in the control group) and did not impact on the overall survival (2-year overall survival was 85.7 ± 7.6 % in the study group and 85.1 ± 7.9 % in the control group).

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Table 1. Changes in peripheral blood leukogram during treatment in control group

Blood cells	Units	Stages of research					Healthy donors
		Before treatment	After operation	After induction course of interferon therapy	3 months after operation	End of treatment	
Leukocytes	$x10^9$/l	5,3 (3,6; 7,3)	6,4 (3,7; 8,9)	4,3 (1,6; 5,3) • 2	4,2 (3,3; 5,3)	5,2 (4,9; 7,0)	5,4 (4,5; 7,0)
Banded neutrophils	%	1,5 (0; 4,5)	2,0 (1,0; 4,5)	2,0 (1,0; 6,5) 1	2,5 (2,5; 3,0) •	1,0 (0,5; 3,0)	1,5 (0; 3,0)
	$x10^9$/l	0,07 (0; 0,29)	0,11 (0,06; 0,40)	0,09 (0; 0,34) 1	0,11 (0,10; 0,13)	0,06 (0,04; 0,15)	0,08 (0; 0,16)
Segmented neutrophils	%	63,0 (44,5; 72,0)	59,0 (52,0; 71,5)	50,0 (33,0; 61,0)	58,5 (49,0; 66,5)	54,5 (48,0; 69,0)	55,5 (42,5; 66,5)
	$x10^9$/l	2,96 (2,04; 5,15)	3,91 (1,96; 5,70)	2,15 (0,78; 3,15) • 1, 2	2,49 (1,71; 3,18)	2,83 (2,30; 4,90)	3,11 (1,95; 4,50)
Eosinophils	%	2,5 (0,5; 6,0)	1,5 (1,0; 5,0)	1,0 (0; 3,0) 1	1,5 (0,5; 5,0)	0,5 (1,0; 5,0)	2,0 (0; 5,5)
	$x10^9$/l	0,14 (0,04; 0,36)	0,10 (0,05; 0,28)	0,04 (0; 0,14) 1	0,08 (0,02; 0,18)	0,04 (0,03; 0,24)	0,12 (0; 0,29)
Basophils	%	1,0 (0; 2,0)	1,0 (0; 2,0)	0 (0; 1,5)	0,7 (0; 1,0)	1,5 (0; 3,0)	1,0 (0; 1,5)
	$x10^9$/l	0,06 (0; 0,11)	0,05 (0; 0,14)	0 (0; 0,06) 1	0,03 (0; 0,05)	0,08 (0; 0,15)	0,05 (0; 0,10)
Monocytes	%	8,0 (5,0; 12,0)	7,5 (4,5; 10,0)	8,0 (4,0; 13,0)	10,0 (6,5; 14,0)	7,0 (6,0; 9,0)	7,0 (4,5; 9,0)
	$x10^9$/l	0,45 (0,12; 0,77)	0,40 (0,21; 0,67)	0,38 (0,06; 0,66)	0,42 (0,21; 0,69)	0,42 (0,36; 0,44)	0,33 (0,23; 0,54)
Large granular lymphocytes	%	2,8 (0,5; 6,0)	3,0 (2,0; 5,0)	4,0 (2,0; 15,0)	4,5 (2,0; 7,0)	4,0 (2,5; 7,0)	4,0 (1,5; 11,0)
	$x10^9$/l	0,16 (0,03; 0,34) •	0,18 (0,11; 0,32)	0,15 (0,09; 0,71)	0,19 (0,07; 0,34)	0,20 (0,13; 0,54)	0,24 (0,11; 0,50)

Lymphocytes	%	22,0 (15,0; 35,0) •	22,0 (19,0; 34,0) •	41,5 (21,0; 52,0)	25,5 (21,5; 32,0)	33,5 (24,0; 34,0)	33,5 (21,5; 46,0)
	x10^9/l	1,32 (0,82; 1,70) •	1,53 (0,92; 2,05)	1,25 (0,75; 1,81) • [2]	1,06 (0,78; 1,57) •	1,72 (1,66; 1,74)	1,77 (1,17; 2,54)

Notes:

1. [1] – differences are statisticaly significant compared with baseline (p< 0,05);

2. [2] – differences are statisticaly significant compared with data after operation (p< 0,05);

3. • – differences are statisticaly significant compared with data of healthy donors (p< 0,05).

Table 2. Changes in peripheral blood leukogram during treatment in study group

Blood cells	Units	Stages of research					Healthy donors
		Before treatment	After operation	After neoadjuvant therapy	3 months after operation	End of treatment	
Leukocytes	x10^9/l	5,1 (2,6; 6,5)	4,1 (3,0; 5,2) •	5,8 (3,6; 8,9) [2]	3,8 (2,8; 4,8) • [3]	4,1 (2,7; 7,7)	5,4 (4,5; 7,0)
Banded neutrophils	%	3 (0; 8)	3 (0; 7)	1 (0; 5,5)	5,5 (2; 10) • [3]	4 (1; 5) [4]	1,5 (0; 3,0)
	x10^9/l	0,15 (0; 0,39)	0,12 (0; 0,36)	0,07 (0; 0,32)	0,18 (0,08; 0,48) •	0,12 (0,05; 0,21)	0,08 (0; 0,16)

Segmented neutrophils	%	59,5 (51,5; 72,5)	52 (37; 64) [1]	63 (55; 68) • [2]	47 (44; 57) [3]	63 (51,5; 83) [2, 4]	55,5 (42,5; 66,5)
	$x10^9$/l	3,34 (1,42; 4,48)	1,73 (1,25; 2,96) • [1]	3,70 (2,21; 5,87) [2]	1,75 (1,32; 2,64) • [3]	2,58 (1,73; 3,98) [2]	3,11 (1,95; 4,50)
Eosinophils	%	2 (1; 3,5)	1 (0; 1,5) • [1]	1 (0; 5,5)	2 (0; 4,5)	3 (0; 8)	2 (0; 5,5)
	$x10^9$/l	0,06 (0,05; 0,27)	0,03 (0; 0,10) • [1]	0,10 (0; 0,32) [2]	0,07 (0; 0,20)	0,12 (0; 0,31)	0,12 (0; 0,29)
Basophils	%	0,5 (0; 2)	0 (0; 0,5) • [1]	0 (0; 1,5)	0 (0; 1)	1 (0; 3)	1 (0; 1,5)
	$x10^9$/l	0,03 (0; 0,08)	0 (0; 0,04) • [1]	0 (0; 0,06) •	0 (0; 0,04) •	0,05 (0; 0,08)	0,05 (0; 0,10)
Monocytes	%	7 (4,5; 12)	8 (6,5; 14) •	7,5 (3; 13)	10 (8; 14) • [3]	6,5 (2; 13)	7 (4,5; 9,0)
	$x10^9$/l	0,33 (0,23; 0,49)	0,35 (0,24; 0,64)	0,50 (0,15; 0,82)	0,44 (0,22; 0,50)	0,34 (0,08; 0,50)	0,33 (0,23; 0,54)
Large granular lymphocytes	%	2,5 (0,5; 5)	4 (1; 11)	3,5 (1,2; 5,5)	5 (3; 7)	2 (1; 5)	4 (1,5; 11)
	$x10^9$/l	0,12 (0,03; 0,23) •	0,18 (0,03; 0,38)	0,17 (0,05; 0,40)	0,22 (0,11; 0,25)	0,08 (0,03; 0,38)	0,24 (0,11; 0,50)
Lymphocytes	%	23,5 (17,5; 32) •	35 (26; 53) [1]	26,7 (17,5; 33,5) • [2]	34 (21; 38)	22 (7; 35,5) • [2, 4]	33,5 (21,5; 46)
	$x10^9$/l	1,33 (0,61; 2,21) •	1,48 (0,68; 2,11)	1,41 (0,76; 2,28)	1,22 (0,92; 1,39) •	0,73 (0,34; 2,73) •	1,77 (1,17; 2,54)

Notes:

1. [1] – differences are statisticaly significant compared with baseline ($p < 0,05$);
2. [2] – differences are statisticaly significant compared with data after neoadjuvant treatment ($p< 0,05$);
3. [3] – differences are statisticaly significant compared with data after operation ($p< 0,05$);
4. [4] – differences are statisticaly significant compared with data after operation ($p< 0,05$);
5. • – differences are statisticaly significant compared with data of healthy donors ($p< 0,05$);