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Cell-mediated and humoral immunity of choroidal melanoma patients after treatment with photocoagulation combined with strontium-90/ yttrium-90 therapy versus transpupillary thermotherapy combined with strontium-90/yttrium-90 therapy

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Purpose: *To compare cell-mediated and humoral immunity characteristics of patients with T1 to T3 CM treated with photocoagulation (PC) combined with strontium-90 (Sr90)/ yttrium-90 (Yt90) brachytherapy (BT)) versus transpupillary thermotherapy (TTT) combined with Sr90/Yt90 BT.*

Material and Methods: *Eighty-seven patients with T1 to T3 CM were included in the study. Group 1 (TTT plus BT) included 31 patients, group 2 (PC plus BT) included 56 patients, and the control group included 44 healthy individuals. Groups were comparable in terms of age, gender and tumor location.*

Results: *The following parameters were significantly increased ($p < 0.009$) in group 1 compared to controls and group 2: leukocytes (by 1.1 thousand cell/µl and 1.3 thousand cell/µl, respectively), absolute counts and percentages of lymphocytes (by 0.6 thousand cell/µl and 1.0 thousand cell/µl, and by 5.5% and 10.3%, respectively), absolute counts of CD3+ T cells (by 376.2 thousand cell/µl and 520.0 thousand cell/µl, respectively), CD4+ T helpers (by 351.2 thousand cell/µl and 362.0 thousand cell/µl, respectively), CD8+ T suppressors (by 125.8 thousand cell/µl and 133.8 thousand cell/µl, respectively). In addition, there was an increase in absolute counts and percentage of phagocytic neutrophils (by 953.0 thousand cell/µl and 18.5%, respectively) compared to controls, absolute counts of CD16+ NK cells compared to controls and group 2 (by 88.5 thousand cell/µl and 119.2 thousand cell/µl, respectively), absolute counts of CD19+ B cells compared to group 2 (by 166.7 thousand cell/µl) and absolute counts of IgA compared to controls (by 0.5 g/l) and IgM compared to controls and group 2 (by 0.4 g/l and 0.7 g/l, respectively). Moreover, the CD4+/CD8+ ratio was by 2.2 increased compared to controls and by 1.0 decreased compared to group 2. In group 1, there was a decrease in the percentages of CD3+ (by 13.3%) and CD4+ (by 14.5%) compared to group 2, and absolute counts of IgG (by 2.0 g/l) compared to controls. The only substantial changes in immunological parameters with treatment were an increase in the percentage of NK cells by 4.3% ($p = 0.02$) in group 1 and a reduction in the percentage of phagocytic neutrophils by 15.8% ($p = 0.0000$) and an increase in IgM by 0.2 g/l ($p = 0.002$) in group 2.*

Conclusion: *We found that, at baseline, patients with T1 to T3 CM had an active immune response to tumor antigens. In addition, they exhibited no statistically significant changes in the parameters of cell-mediated and humoral immunity after treatment with TTT (delivered using the developed methodology) combined with Sr90/Yt90 BT, excepting an increase in the percentage of NK cells by 4.3% ($p = 0.02$).*

Keywords:

choroidal melanoma, transpupillary thermotherapy, photocoagulation, brachytherapy, immunology, oncology, radiology, choroid

Introduction

The response of the patient's immune system to the treatment of choroidal melanoma (CM) is an important factor, especially given the fact that the eye is an immune privileged site [1] that elicits no inflammatory immune response, which in turn limits the immune-mediated mechanisms of protection from the tumor. In addition, a low mutation load in CM compared to melanoma of other locations (e.g., cutaneous melanoma) may result in an inadequate number of potential neoepitopes for effective anti-tumor immunity [1] and reduction in the immunogenicity of CM. Studies found a direct correlation of various immune characteristics of the CM patient with tumor prognosis [3-11].

Surgical intervention (from local endoresection to enucleation), radiotherapy (brachytherapy, proton therapy, cyber knife or gamma knife) and light energy procedures (photocoagulation, laser coagulation, transpupillary thermotherapy, photodynamic therapy) may be used in the treatment for CM. Although over 90% of patients with CM

can be successfully treated with the above methods, 50% of patients may develop methastasis, which affects the survival of these patients [12-15].

There is a notion that under certain conditions, the immune system does not reject the tumor, but is involved in its development and progression [16]. Adequate organ-saving treatment for CM as well as CM treatment efficacy monitoring requires establishing the pattern of interaction between immunocompetent cells and tumor cells.

The purpose of this study was to compare cellular and humoral immunity characteristics of patients with T1 to T3 CM treated with light energy procedures, photocoagulation (PC) plus strontium-90 (Sr90)/ yttrium-90 (Yt90) brachytherapy (BT)) versus transpupillary thermotherapy (TTT) plus Sr90/Yt90 BT.

Material and Methods

Eighty-seven patients with T1 to T3 CM who received an eye-preserving treatment with either PC plus Sr90/Yt90 BT or TTT (delivered using the developed methodology) plus Sr90/Yt90 BT were included in the study. Group 1 included 31 patients with T1 to T3 CM who were treated with TTT (delivered using the developed methodology) plus Sr90/Yt90 BT. Group 2 included 56 patients with T1 to T3 CM who were treated with PC plus Sr90/Yt90 BT. Group 3 (the control group) included 44 healthy individuals.

Group 1 consisted of 19 women (61.3%) and 12 men (38.7%), with a mean age (standard deviation (SD)) of 50.9 (16.0) years and the age ranging from 15 to 75 years. The right eye was affected in 12 patients (38.7%), and the left eye was affected in 19 patients (61.3%). Group 2 consisted of 20 women (35.7%) and 36 men (64.3%), with a mean age (SD) of 53.6 (12.0) years and the age ranging from 19 to 77 years. The right eye was affected in 34 patients (60.7%), and the left eye was affected in 22 patients (39.3%). Group 3 consisted of 23 women (52.3%) and 21 men (47.7%), with a mean age (SD) of 54.3 (13.0) years and the age ranging from 21 to 74 years. Groups were similar with respect to gender, age and tumor location.

Treatment with PC plus Sr90/Yt90 BT was delivered using well-known methodologies [3-5]. Treatment with TTT plus Sr90/Yt90 BT was performed in the following way: after TTT was delivered using the developed methodology [17], Sr90/Yt90 BT was performed under general anesthesia in the form of two surgical interventions: beta-ray applicator suturing to the sclera in the projection of the tumor, and beta-ray applicator removal 5 to 10 days (mean time, 6.0 ± 3.0 days) thereafter, depending on the calculated dose of radiation for the tumor apex [3-5].

Immunological study was conducted at immunology laboratory using routine methods [18, 19] to determine the following peripheral blood characteristics: absolute counts of leukocytes and lymphocytes, absolute counts and percentages of CD3+ T cells, CD4+ T helpers, CD8+ T suppressors, CD19+ B cells, and CD16+ natural killer (NK) cells [20]. In addition, phagocytic neutrophil activity (PNA), numbers and percentages of active rosette-forming T-cells (ARFC) and imminoglobulins (Ig) A, M and G were evaluated [21].

Fasting blood samples were taken before treatment and on the next day on completion of treatment.

This study involved human subjects and followed ethical standards as outlined in the 1964 Declaration of Helsinki of the World Medical Association with its further amendments and the European Convention on Human Rights and Biomedicine, and relevant laws of Ukraine. This study is part of the research project "To Examine the Pathogenetic Mechanisms of the Clinical Effect of (Response to) Combination Treatment for Medium and Large Uveal Melanomas and Malignant Lesions of the Palpebral Conjunctiva, Semilunar Fold and Caruncle" (state registration number, 01224U00149). The study was approved by the bioethics committee of SI "The Filatov Institute of Eye Diseases and Tissue Therapy of the National Academy of Medical Sciences of Ukraine" (committee minutes dated October 24, 2024), and informed consent was obtained from subjects.

Data were analyzed using JASP (The JASP Team, Amsterdam, the Netherlands). Mean and SD values were calculated.

For comparisons involving quantitative parameters in more than two groups, one-way analysis of variance with post-hoc Newman-Keuls tests were used. P values ≤ 0.05 were considered significant.

Results

Table 1 compares groups of patients with different stages of CM versus controls for the pre-treatment parameters of humoral and cell-mediated immunity. The following parameters were significantly increased in group 1 (TTT plus BT) compared to controls and group 2: leukocytes (by 1.1 thousand cell/µl, p = 0.0003 and 1.3 thousand cell/µl, p = 0.0000, respectively), absolute counts and percentages of lymphocytes (by 0.6 thousand cell/µl, p = 0.002, 1.0 thousand cell/µl, p = 0.0000 and by 5.5%, p=0.004 and 10.3%, p = 0.0000, respectively), absolute counts of CD3+ T cells (by 376.2 thousand cell/µl, p = 0.009 and 520.0 thousand cell/µl, p = 0.0000, respectively), CD4+ T helpers (by 351.2 thousand cell/µl, p = 0.003 and 362.0 thousand cell/µl, p = 0.0002, respectively), and CD8+ T suppressors (by 125.8 thousand cell/µl, p = 0.001 and 133.8 thousand cell/µl, p = 0.0002, respectively). In addition, there was an increase in absolute counts and percentage of phagocytic neutrophils (by 953.0 thousand cell/µl and 18.5%, p = 0.0001 respectively) compared to controls, absolute counts of CD16+ NK cells compared to controls and group 2 (by 88.5 thousand cell/µl, p = 0.003 and 119.2 thousand cell/µl, p = 0.01), absolute counts of CD19+ B cells compared to group 2 (by 166.7 thousand cell/µl, p = 0.0000), absolute counts of IgA compared to controls (by 0.5 g/l, p = 0.000), and IgM compared to controls and group 2 (by 0.4 g/l and 0.7 g/l, respectively, p = 0.0000). Moreover, the CD4+/CD8+ ratio was by 2.2 increased compared to controls (p = 0.0000) and by 1.0 decreased compared to group 2 (p = 0.007).

Table 1. Comparing groups of patients before treatment with photocoagulation combined with brachytherapy (group 2) versus transpupillary therapy combined with brachytherapy (group 1) for choroidal melanoma and healthy controls (group 3) for immunity parameters (mean (standard deviation))

Immunity parameters	Study groups			p
	Group 1, n=31	Group 2, n=56	Control group, n=44	
White blood cell count (thousands of cells/μl)	6.6 (1.3) ↑	5.3 (1.2) ↓	5.5 (1.2)	P_{1-2}=0.0000 P_{1-3}=0.0003 P_{2-3}=0.41
Lymphocyte count (thousands of cells/ μl)	2.2 (0.7) ↑	1.2 (0.4) ↓	1.6 (0.6)	P_{1-2}=0.0000 P_{1-3}=0.002 P_{2-3}=0.0001
Lymphocyte percentage	33.4 (9.0) ↑	23.1 (5.5) ↓	27.9 (6.9)	P_{1-2}=0.0000 P_{1-3}=0.004 P_{2-3}=0.0002
CD3+ T-cell count (thousands of cells/ μl)	1492.3 (653.4) ↑	972.3 (386.6) ↓	1116.1 (558.3)	P_{1-2}=0.0000 P_{1-3}=0.009 P_{2-3}=0.13
Percentage of CD3+ T-cells	66.2 (11.9) ↓	79.5 (12.3) ↑	69.7 (10.5)	P_{1-2}=0.0000 P_{1-3}=0.18 P_{2-3}=0.0001
CD4+ T-helper count (thousands of cells/ μl)	1157.3 (513.2) ↑	795.3 (347.7) ↓	806.1 (454)	P_{1-2}=0.0002 P_{1-3}=0.003 P2-3=0.89
Percentage of CD4+ T-helper cells	50.1 (12.6) ↓	64.6 (13.3) ↑	49.0 (12)	P_{1-2}=0.0000 P_{1-3}=0.71 P_{2-3}=0.0000
Cytotoxic CD8+ T-cell count (thousands of cells/ μl)	320.0 (195.2) ↑	186.2 (126.2) ↓	194.2 (132.5)	P_{1-2}=0.0002 P_{1-3}=0.001 P_{2-3}=0.76
Percentage of cytotoxic CD8+ T-cells	15.4 (8.5) ↑	14.3 (4.4) ↓	16.5 (4.6)	P_{1-2}=0.43 P_{1-3}=0.47 P_{2-3}=0.02
CD4+/CD8+ ratio	3.9 (1.2) ↓	4.9 (1.8) ↑	1.7 (1.3)	P_{1-2}=0.007 P_{1-3}=0.0000 P_{2-3}=0.0000
CD19+ B cell count (thousands of cells/ μl)	277.1 (123.6) ↑	109.4 (86.9) ↓	233.9 (110.7)	P_{1-2}=0.0000 P_{1-3}=0.12 P_{2-3}=0.0000
Percentage of CD19+ B cells	12.9 (4.6) ↑	9.2 (6.1) ↓	14.5 (4.7)	P_{1-2}=0.08 P_{1-3}=0.57 P_{2-3}=0.007
Phagocytic neutrophil activity (thousands of cells/ μl)	3013.9 (913.0) ↑	3012.4 (959.8) ↑	2060.9 (1028.0)	P_{1-2}=0.99 P_{1-3}=0.0001 P_{2-3}=0.0000
Percentage of phagocytic neutrophil activity	73.1 (14.5) ↑	76.7 (5.9) ↑	54.6 (21.3)	P_{1-2}=0.11 P_{1-3}=0.0001 P_{2-3}=0.0000
CD16+ NK cell count (thousands of cells/ μl)	260.0 (162.4) ↑	140.8 (82.1) ↓	171.5 (87.2)	P_{1-2}=0.01 P_{1-3}=0.003 P_{2-3}=0.25
Percentage of CD16+ NK cells	11.5 (4.6)	12.1 (4.4) ↑	11.4 (4.2)	P_{1-2}=0.68 P_{1-3}=0.92 P_{2-3}=0.59

Table 1. (continued)

Immunity parameters	Study groups			p
	Group 1, n=31	Group 2, n=56	Control group, n=44	
IgA(0), g/l	2.6 (1.0) ↑	2.5 (0.7) ↓	2.1 (0.6)	P_{1-2}=0.71 P_{1-3}=0.009 P_{2-3}=0.03
IgM(0), g/l	1.2 (0.4) ↑	0.5 (0.2) ↓	0.8 (0.2)	P_{1-2}=0.0000 P_{1-3}=0.0000 P_{2-3}=0.0000
IgG(0), g/l	11.4 (2.8) ↓	12.1 (3.5) ↓	13.4 (2.9)	P_{1-2}=0.38 P_{1-3}=0.003 P_{2-3}=0.14

Note: n, number of patients; p, level of significance by the Newman-Keuls test; ↑, the mean parameter value is higher than in another group; ↓, the mean parameter value is lower than in another group; NK, natural killers; Ig, immunoglobulin

In group 1, there was a decrease in the percentages of CD3+ (by 13.3%, p = 0.0000) and CD4+ (by 14.5%, p = 0.000) compared to group 2, and absolute counts of IgG (by 2.0 g/l, p = 0.003) compared to controls.

Table 2 compares group 1 and group 2 in terms of pre-treatment and post-treatment immunological parameters. In group 1 (TTT plus BT), there was no substantial changes in immunological parameters with treatment, excepting an increase in the percentage of NK cells by 4.3% (p = 0.02). In group 2 (PC plus BT), the only substantial changes in immunological parameters with treatment were a reduction in the percentage of phagocytic neutrophils by 15.8% (p = 0.0000) and an increase in IgM by 0.2 g/l (p = 0.002). There was, however, a statistically significant increase in the majority of parameters in group 1 compared to group 2. Therefore, the tumor process in patients with T1 to T3 CM is impacted by changes in the immune status, which is reflected by increases in the parameters of cell-mediated immunity (CD3+, CD4+, CD8+ and CD16+) and humoral immunity (absolute counts of CD19+), and body resistance to tumor growth (absolute counts and percentages of phagocytic neutrophils).

Table 2. Comparing groups of patients before and after treatment with photocoagulation combined with brachytherapy (group 2) versus transpupillary therapy combined with brachytherapy (group 1) for choroidal melanoma for immunity parameters (mean (standard deviation))

Immunity parameters	Group 1, n = 31		Group 2, n = 56		p
	Before treatment (1)	After treatment (2)	Before treatment (3)	After treatment (4)	
White blood cell count (thousands of cells/μl)	6.6 (1.3) ↑	6.1 (1.6) ↑	5.3 (1.2)	5.3 (1.4)	p_{1-2}=0.29 p_{3-4}=1.0 p_{2-4}=0.1
Lymphocyte count (thousands of cells/ μl)	2.2 (0.7) ↑	2.2 (0.7) ↑	1.2 (0.4)	1.2 (0.3)	p_{1-2}=1.0 p_{3-4}=1.0 p_{2-4}=0.0000
Lymphocyte percentage	33.4 (9.0) ↑	37.3 (9.1) ↑	23.1 (5.5)	22.5 (5.7)	p_{1-2}=0.14 p_{3-4}=0.61 p_{2-4}=0.0000
CD3+ T-cell count (thousands of cells/ μl)	1492.3 (653.4) ↑	1424.8 (514.6) ↑	972.3 (386.6)	979.4 (314.9)	p_{1-2}=0.75 p_{3-4}=0.92 p_{2-4}=0.0006
Percentage of CD3+ T-cells	66.2 (11.9) ↓	63.9 (10.7) ↓	79.5 (12.3)	83.5 (9.4)	p_{1-2}=0.56 p_{3-4}=0.09 p_{2-4}=0.0000
CD4+ T-helper count (thousands of cells/ μl)	1157.3 (513.2) ↑	1121.3 (461.2) ↑	795.3 (347.7)	798.9 (276.2)	p_{1-2}=0.83 p_{3-4}=0.96 p_{2-4}=0.004

Table 2. (continued)

Immunity parameters	Group 1, n = 31		Group 2, n = 56		p
	Before treatment (1)	After treatment (2)	Before treatment (3)	After treatment (4)	
Percentage of CD4+ T-helper cells	50.1 (12.6) ↓	50.0 (11.6) ↓	64.6 (13.3)	68.3 (11.7)	p_{1-2}=0.16 p_{3-4}=0.98 p_{2-4}=0.0000
Cytotoxic CD8+ T-cell count (thousands of cells/ μl)	320.0 (195.2) ↑	278.4 (75.2) ↑	186.2 (126.2)	175.7 (104.6)	p_{1-2}=0.67 p_{3-4}=0.48 p_{2-4}=0.003
Percentage of cytotoxic CD8+ T-cells	15.4 (8.5) ↑	12.8 (2.3) ↓	14.3 (4.4)	14.8 (5.8)	p_{1-2}=0.31 p_{3-4}=0.63 p_{2-4}=0.25
CD4+/ CD8+ ratio	3.9 (1.2) ↓	4.1 (1.4) ↓	4.9 (1.8)	5.3 (1.9)	p_{1-2}=0.49 p_{3-4}=0.3 p_{2-4}=0.05
CD19+ B cell count (thousands of cells/ μl)	277.1 (123.6) ↑	273.0 (71.9) ↑	109.4 (86.9)	99.9 (115.3)	p_{1-2}=0.91 p_{3-4}=0.65 p_{2-4}=0.0000
Percentage of CD19+ B cells	12.9 (4.6) ↑	12.5 (3.2) ↑	9.2 (6.1)	7.1 (4.5)	p_{1-2}=0.78 p_{3-4}=0.07 p_{2-4}=0.0003
Phagocytic neutrophil activity (thousands of cells/ μl)	3013.9 (913.0)	2657.5 (1195.1) ↓	3012.4 (959.8)	3191.6 (1335.3)	p_{1-2}=0.29 p_{3-4}=0.45 p_{2-4}=0.22
Percentage of phagocytic neutrophil activity	73.1 (14.5) ↓	72.3 (16.2)	76.7 (5.9)	61.4 (10.3)	p_{1-2}=0.88 p_{3-4}=0.0000 p_{2-4}=0.008
CD16+ NK cell count (thousands of cells/ μl)	260.0 (162.4) ↑	377.1 (184.0) ↑	140.8 (82.1)	119.8 (63.9)	p_{1-2}=0.16 p_{3-4}=0.54 p_{2-4}=0.001
Percentage of CD16+ NK cells	11.5 (4.6) ↓	15.8 (5.1) ↑	12.1 (4.4)	12.9 (4.1)	p_{1-2}=0.02 p_{3-4}=0.68 p_{2-4}=0.19
IgA (0), g/l	2.6 (1.0) ↑	2.8 (0.8) ↑	2.5 (0.7)	2.3 (1.2)	p_{1-2}=0.54 p_{3-4}=0.49 p_{2-4}=0.25
IgM (0), g/l	1.2 (0.4) ↑	1.3 (0.3) ↑	0.5 (0.2)	0.7 (0.2)	p_{1-2}=0.44 p_{3-4}=0.002 p_{2-4}=0.0000
IgG (0), g/l	11.4 (2.8) ↓	11.9 (2.6)	12.1 (3.5)	11.7 (2.8)	p_{1-2}=0.60 p_{3-4}=0.75 p_{2-4}=0.86

Note: n, number of patients; p, level of significance by the Newman-Keuls test; ↑, the mean parameter value is higher than in another group before or after treatment; ↓, the mean parameter value is lower than in another group before or after treatment; NK, natural killers; Ig, immunoglobulin

Discussion

We found that, at baseline, patients with T1 to T3 CM had an active immune response to tumor antigens, which resulted in changes in activation of peripheral blood lymphocytes. This is in agreement with findings of other studies [3-6, 17].

Complex interactions develop among different lymphocyte subsets. A statistically significant decrease in the activity of effectors of cytotoxic activity of CD8+ T suppressors in CM patients treated with PC plus BT has been reported previously [3-5]. In the current study, however, this parameter was significantly increased in CM pa-

tients treated with TTT plus BT compared to controls and CM patients treated with PC plus BT ($p = 0.001$ and $p = 0.0002$, respectively).

Therefore, the level of lymphocyte activation with TTT combined with BT treatment is different from PC combined with BT treatment. Different effects from PC and TTT cause different immune responses both directly in tumor tissues and in the patient's immune status, reflecting the anti-tumor reactivity of the body.

It should be noted, however, that our two groups of patients differed not only in treatment received, but they were formed and treated in different long periods. Patients in group 1 received their TTT plus BT treatment in 2021-2024, the period after COVID-19 pandemic and the period of war in Ukraine, which also affected their immunity status. Unfortunately, to the best of our knowledge, there is no literature data that can be compared with our results. Research on the mechanisms of interaction between tumor and immunocompetent cells is important for understanding the processes of implementation of the curative effect of eye-preserving treatment (particularly, TTT plus BT) for CM, especially for understanding the feasibility of administration of immune-modulating therapy, and determining the prognosis for metastasis and survival [22-26].

Conclusion

We found that, at baseline, patients with T1 to T3 CM had an active immune response to tumor antigens. In addition, they exhibited no statistically significant changes in the parameters of cell-mediated and humoral immunity after treatment with TTT (delivered using the developed methodology) combined with Sr90/Yt90 BT, excepting an increase in the percentage of NK cells by 4.3% ($p = 0.02$).

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Data Availability Declaration: *All the data obtained or examined during this study has been incorporated into this published article.*

Abbreviations: *BT, brachytherapy; CM, choroidal melanoma; Ig, immunoglobulin; NK, natural killers; PC, photocoagulation; PNA, phagocytic neutrophil activity; TTT, transpupillary thermotherapy*