



Reasonability of Carrying out Intra-Arterial Selective Chemotherapy (Cisplatin) in Combination with Photodestruction, Brachytherapy and Interferon Therapy in Patients with Uveal Melanoma

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Abstract

Purpose: To study the effectiveness of selective intra-arterial chemotherapy (SICA) (cisplatin) in combination with photodestruction, brachytherapy (BT) and interferon therapy (IFT) in patients with UM of the eye.

Methods: The analysis was carried out in 238 patients (men - 99, women - 139) who received the following treatment methods as organ-preserving treatment for patients with UM: transpupillary thermotherapy (TTT), BT, IFT and SIAC.

Results: The results of clinical studies allow us to note that the inclusion of selective intra-arterial chemotherapy (cisplatin) in the complex of organ-preserving treatment of UM made it possible to activate the dynamics of tumour regression after 6 and 12, as well as the reliability in relation to the control group was $P < 0.06$ and $P < 0.06$, in accordance. It should be noted that the dynamics of tumour regression in the study group (TTT, BT, IFT and SIAC) after two years was more active compared to the control group of patients and complete regression was 39.4%, while in the control group it was 25.7%. The obtained preliminary data on the effectiveness of TTT, BT, IPT and SIAC in patients with UM do not allow us to speak unequivocally about the rational dose of cisplatin and the choice of cytostatic. We can assert the expediency of the chosen approach to complex therapy of UM.

Conclusion: Conducting SIAC (cisplatin) in combination with TTT, BT and IFT in patients with UM increases the sensitivity of tumour cells to photodestruction and local radiotherapy, which promotes more active tumour regression.

Keywords: Uveal Melanoma; Organ-Sparing Treatment; Intra-Arterial Chemotherapy

Key Messages

- What is Known:** In ophthalmooncology there are a few scientific articles on adjuvant treatment methods to increase the radiosensitivity of uveal melanoma cells. The authors used cisplatin for intravenous chemotherapy, there were negative side effects.

- What is New:** To prevent these negative side effects and increase the effectiveness of the antitumor cisplatin, we were the first to use intra-arterial chemotherapy cisplatin in the temporal artery in patients with uveal melanoma, which allowed us to create a higher concentration of cisplatin in uveal melanoma; We established for the first time that the addition to the

complex of organ-preserving treatment of UM (SICA) (cisplatin) allowed to activate the dynamics of tumor regression after 6 and 12 months; SICA chemotherapy made it possible to achieve complete regression of UM in 39.4% versus 25.7%.

Abbreviations

UM: Uveal Melanoma; TTT: Transpupillary Thermotherapy; BT: Brachytherapy; IF: Recombinant Alpha-2b Interferon; IFT: Interferon Therapy; SIAC: Selective Intra-Arterial Chemotherapy.

Introduction

Uveal melanoma occurs as a result of malignant transformation of melanocytes of the vascular membrane of the eyeball and poses a threat not only to the organ of vision, but also to the patient's life. Thus, 50% of patients at different times, regardless of the method of treatment of the primary tumour, develop a metastatic disease. Factors of unfavourable prognosis in UM include: age of patients, size of primary tumour, cell composition (epithelioid or mixed histological type of cells), extraocular growth, chromosomal changes (monosomy of chromosome 3 and/or amplification of chromosome 8) [1]. UM metastasizes hematogenously, most often in the liver (90%), lungs (25%), bones (15%), skin (10%) [2]. The median life expectancy for liver metastases in patients with UM is 9 months, and in the group of patients with extrahepatic manifestations it is 19-28 months [3]. To date, two main directions in the approaches to the therapy of UM of the eye have been clearly defined, i.e. eye enucleation and organ-preserving treatment.

Methods using light energy in the treatment of patients with UM are a great achievement of modern ophthalmic oncology. This applies to the use of xenon photocoagulation and laser irradiation. However, as noted by a number of authors Terentyeva LS, et al. [4,5], with the help of xenon photocoagulation, it is possible to destroy a tumour with a protrusion of no more than 2 mm. And with an area of no more than 4 diameters of the optic nerve disc, and when applying laser irradiation with a wavelength of 1.06 microns, it is possible to destroy a tumour with a protrusion of up to 4 mm [6]. However, the dominant number of tumours are medium and large with persistence and extent of 80-85% [7,8]. In order to expand the organ-preserving treatment of uveal melanoma, we used the simultaneous use of photodestruction and BT, which made it possible to achieve a clinical result of UM with a prominence of up to 8.0 mm, while BT alone - only up to 5.0 mm [4,7,9]. A significant point in conducting organ-sparing treatment is that in 41-52% of cases it is possible to preserve visual functions, which is very important in the presence of a tumour in one eye [7,10].

Various approaches have been proposed to increase the efficiency of photodestruction, including the use of interferons [7,9,11] and cytostatics, which increase the sensitivity of tumour cells to radiation [12,13]. However, during systemic chemotherapy (cisplatin), side effects in the form of dyspepsia, nausea, vomiting, leuco- and thrombopenia, etc. are observed. To prevent the above-mentioned negative side effects of chemotherapy and increase the effectiveness of its anti-tumour effect, in our opinion, selective intra-arterial chemotherapy (SIAC) can be used in patients with uveal melanoma. With SIAC, the drug enters the capillary network of the tumour, while the concentration of the drug in the tumour tissues increases and decreases in healthy tissues - in comparison with intravenous injections. Thus, it appears to us to study the role of adjuvant SIAC (cisplatin) in combination with TTT, BT and IFT, which may be of both scientific and practical interest.

Methods

The analysis was carried out on 238 patients who represented the following clinical groups according to the nature of the treatment.

- **The First (Control) Group** consisted of 33 patients (11 (33.3%) men, 22 (66.7%) women who underwent TTT, BT, IFT and SIAC (cisplatin) as organ-preserving therapy for uveal melanoma. In 18 (54.5%) cases had the right eye, and 15 (45.5%) - the left. It is important to note that in 8 (24.2%) cases the tumour was non-pigmented, in 16 (48.5%) - weakly pigmented and in 9 (27.3%) cases - intensively pigmented.
- **The Second (Control) Group** consisted of 205 patients (men - 88 (42.9%) and women - 117 (57.1%). In 103 (50.2%) cases there was a right eye, and in 102 (49.8%) - left. It is important to note that in 4 (1.9%) cases the tumour was non-pigmented, in 163 (79.6%) it was weakly pigmented and in 38 (18.5%) it was intensely pigmented.

Methodology of conducting TTT, BT, IFT and SIAC (cisplatin)

Transpupillary Thermotherapy

With using a diode laser (810 nm) in continuous mode with an exposure of 60-90 seconds, with a power of 200-1200 mW and a light spot diameter of 1.5-7 mm. The number of sessions per course is up to 4, with an interval of 3-4 months between courses. TTT was performed on a diode laser manufactured by Quantel Medical.

Methods of Brachytherapy

After general or local anesthesia, the boundaries of the tumour were determined using diaphanoscopy, and then a beta-applicator (strontium - 90 + yttrium - 90) Gy was sewn

to the sclera at the base of the tumour. The diameter of the beta applicator was selected so as to completely cover the base of the tumour, as well as the surrounding healthy tissue around the tumour with a width of 2 mm. The duration of radiation therapy ranged from 3 to 10 days and depended on the size of the tumour and the type of beta-applicator. The total radiation doses were on average (2295 + 240 Gy).

Method of Administration of Alpha-2b-Interferon (Laferobion)

In patients with uveal melanoma of the eye. Laferobion was administered parabolbar daily at 1 million IU (diluted in 1 ml of water for injections) for 10 days; repeated 10-day

administrations were carried out after 20 days, twice; the total course of Laferobion was 30 million IU.

The Technique of Selective Intra-Arterial Chemotherapy (SIAC)

SIAC was that the catheter was retrogradely inserted through the external temporal artery (to a depth of 2-3 cm) to the mouth of the maxillary artery (Figure 1). The position of the catheter during the operation was controlled with the help of a 0.5% solution of methylene blue, which, after being inserted into the catheter (0.5-0.7 ml), stained the area of tissue corresponding to the blood supply zone of the maxillary artery.

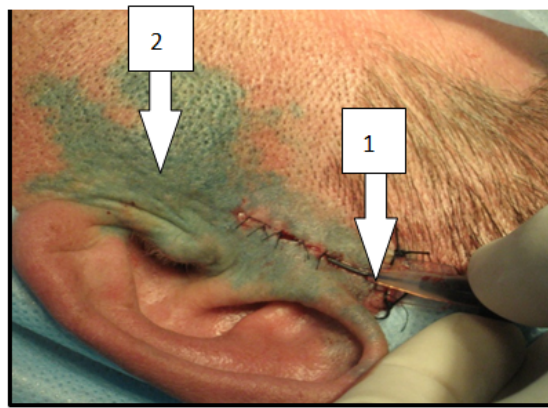


Figure 1: A: Catheter is put into temporal artery; B. Control of its position with the help of 0,5% solution methylenum coeruleum.

In addition, before the infusion of cisplatin, a control angiography was performed to determine the correct

position of the catheter (Figure 2).

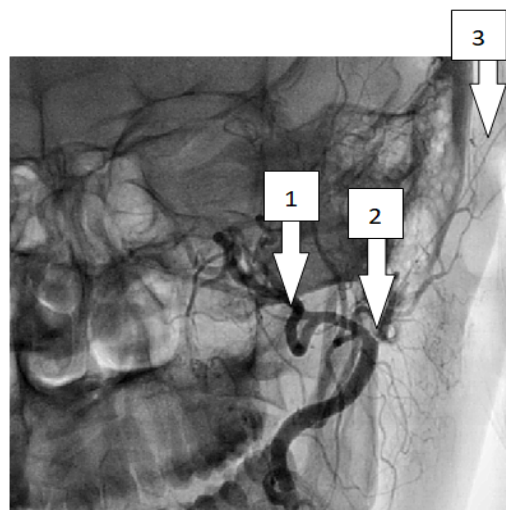


Figure 2: Control angiography (1 - a. maxillaris, 2, 3 - catheter in a. temporalis superficialis).

The course of chemotherapy consisted of 6-10 intra-arterial infusions of cisplatin into the temporal artery ($SD = 69.4 + 12.6$) mg.

The Evaluation of the Effectiveness of the Treatment

It was carried out at the end of two years after the start of the treatment. Complete or partial stabilization of tumour growth was evaluated as a positive result, and continued tumour growth as a lack of clinical effect.

Methods

To assess the statistical significance of the differences between the comparing clinical groups, the parametric

t-Student and F-Fisher tests were used at the confidence level of $p=0.95$. Statistical data analysis was performed using algorithms implemented in the Statistica 5.0 program package [14].

Results

First of all, a comparative analysis of 33 patients who underwent TTT, BT, IFT and SIAC (cisplatin) as organ-preserving therapy with UM of the eye (the average tumor size before treatment was 6.75 ± 0.32 mm) and with a control group of patients with UM (205 patients, the average tumor size before treatment was 6.49 ± 0.14 mm.) who underwent TTT, BT and IFT as organ-preserving therapy (Figure 3).

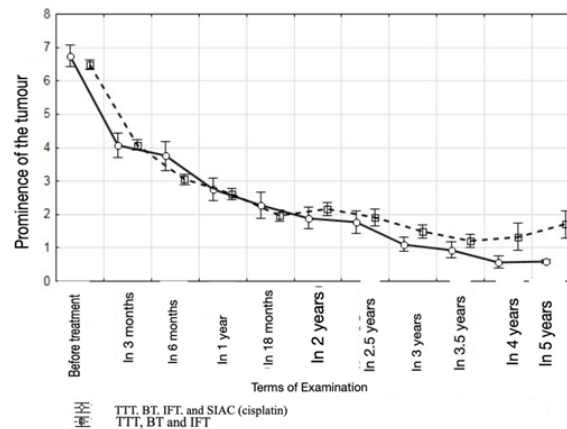


Figure 3: Comparative analysis of the dynamics of regression from UM of the eye in patients who underwent TTT+BT+IFT+SIAC (cisplatin) and in the control group who underwent TTT, BT and IFT as organ-preserving treatment.

On the presented graph (Figure 3), it can be noted that the regression of the intraocular tumour in the group of patients who underwent SIAC (cisplatin) in combination with TTT, BT and IPT was more active, especially in the first 6 and 12 months, and the reliability was $P < 0.06$ and $P < 0.06$ in

relation to the control group, which underwent only TTT, BT and IFT. It should be noted that in the course of TTT, BT, IFT and SIAC in patients with UM of the eye, the following types of clinical reaction of the tumour to the therapeutic action were noted, Table 1.

№	Nature of treatment	The nature of the clinical reaction of the tumor for treatment Number of patients in %			
		Full regression	Partial regression	Стабілізація росту	Continued growth
1	TTT, BT, IFT and SIAC (cisplatin) n = 33	13 (39,4%)	11 (33,3%)	6 (18,2%)	3 (9,1%)
2	TTT, BT, IFT n = 205	58 (25,7%)	137 (60,9%)	9 (4,1%)	21 (9,3%).

N - Number of patients

Table 1: Comparative analysis of the clinical response of the tumor during organ-sparing treatment (TTT, BT, IFT and SIAC (cisplatin) and TTT, BT and IFT) in patients with UM of the eye.

From the data presented in the table 1, it can be noted that the positive clinical result (complete, partial regression and stabilization of tumour growth) in patients who were included in the complex of treatment with SIAC (cisplatin) was 90.9%

and it practically did not differ from the control group, which only underwent TTT, BT and IFT. It is important to note that the dynamics of tumour regression in the study group (TTT, BT, IFT and SIAC) after two years was more active compared

to the control group of patients and complete regression was 39.4%, while in the control group it was 25.7 %. It is known that the clinical evaluation of organ-preserving therapy for choroidal melanoma was carried out two years after the start of treatment. The obtained preliminary data on the effectiveness of TTT, BT, IFT and SIAC in patients with UM of the eye do not allow us to talk unambiguously about the rational dose of cisplatin, as well as the choice of cytostatics. We can affirm the feasibility of the selected approach in complex therapy in patients with UM of the eye.

Discussion

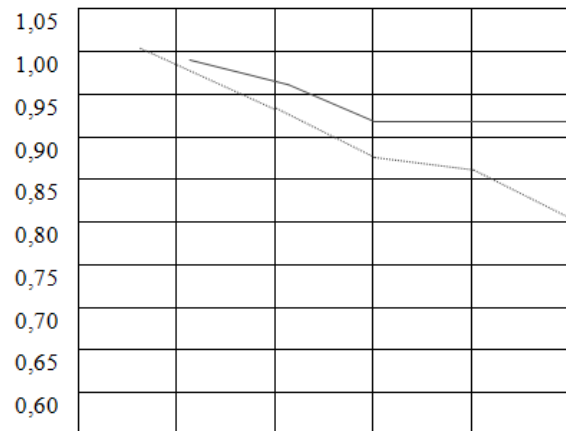
Intraocular tumours occupy an important place among neoplasms of the organ of vision, second in frequency only to tumours of the eyelids. Due to their high malignancy, UM represent a threat not only to the organ of vision, but also to the life of the patient [2,11]. Thus, timely diagnosis and pathogenetically oriented treatment of UM melanoma is of important medical and social importance, and the search and development of rational methods of therapy for patients with this ophthalmopathy are relevant. Terentyeva LS, et al. [4] carried out an analysis of the effectiveness of organ-preserving treatment with UM melanoma of the eye using xenon photocoagulation (XFC) and BT which showed that the size and localization of the tumour does not always play a decisive role in the exact predicted nature of the clinical response of melanoma to the treatment. The authors came to the conclusion that a more accurate prediction of the effectiveness of organ-sparing treatment is possible only with comprehensive consideration of many characteristics of tumours, including the cell type of melanoma, the degree of pigmentation, localization, and features of the body's immunoreactivity.

In recent decades, photodestruction (xenon photocoagulation, laser coagulation, and TTT) has been used as an organ-preserving treatment method for UM. However, intraocular tumours with a protrusion of no more than 2.5-3.5 mm can be destroyed by the above methods, and their prevalence is 20-25% of all tumours [4,5]. The simultaneous use of photodestruction and BT made it possible to achieve a clinical result in UM with a prominence of up to 8.0 mm, while independent BT - only up to 5.0 mm [9]. In the following years, cytokines (interleukins, interferons) are widely used in oncology in combination with other methods of treatment [1]. In order to expand the indications for organ-preserving treatment with UM of the eye, it is possible to increase the sensitivity of tumour cells to therapeutic factors (XFC and BT) by including recombinant alpha-2b-interferon (IF) in a complex with selective intra-arterial chemotherapy (SIAC) (cisplatin). We conducted an analysis of the effectiveness of a complex approach to organ-preserving treatment in patients

with UM of the eye using IFT and selective intra-arterial chemotherapy (cisplatin). Analysis of the results of a study that was conducted in 238 patients with uveal melanoma. In 33 patients with UM of the eye, who underwent TTT, BT, IFT, and SIAC (cisplatin), and in 205 patients, complex antitumour therapy without SIAC was performed.

A comparative analysis of the data on SIAC (cisplatin) in combination with TTT, BT and IFT in patients with UM allows us to conclude that, despite the higher final parameters of tumour persistence, its regression took place more actively at the end of 6 and 12 months (Figure 3). The obtained data on the use of SIAC (cisplatin) allow us to conclude that the sensitivity of UM cells to light energy and local radiotherapy is increased, which is consistent with the results of research by other authors Panova IE, et al. [12,13]. It seems to us that SIAC avoids the side effects that occur during systemic chemotherapy (cisplatin). In the case of SIAC, the drug enters the capillary network of the tumour, while we create a therapeutic dose of the drug in the tumour tissues and reduce it in healthy tissues - in comparison with intravenous infusion [13]. The obtained preliminary results of SIAC (cisplatin) in combination with photodestruction and BT are the subject of optimization of SIAC technology, both in the way of finding adequate chemopreparations and in the way of their rational total doses. In order to determine the effect of SIAC (cisplatin) in combination with TTT, BT and IFT on the prognosis of life of patients with uveal melanoma, we conducted a comparative analysis of the survival of patients with this pathology in dynamics for 60 months. The control group consisted of 205 patients with UM, who were treated with TTT, BT and IFT as organ-preserving treatment. The analysis of both clinical groups was carried out using the Kaplan-Meier method. The results of this analysis are presented in Figure 4.

Comparative analysis of the data presented in Figure 4 shows that the patients who underwent SIAC (cisplatin) in combination with TTT+BT and IFT had a more favorable prognosis for life in the period of 36-60 months, however, as statistical analysis showed, no significant differences were noted during the entire observation period (Cex F-Test = 1.24, P = 0.29). It should be noted that the curves shown in Figure **** reflect only the survival of patients in different periods from the onset of the disease, and as for the survival rate, it was 90% for the group of patients who underwent SIAC (cisplatin) + TTT+BT and IFT, and 84.9% in the control group. Thus, a comprehensive approach to conducting organ-preserving treatment in patients with UM of the eye, taking into account clinical criteria, as well as the appointment of pathogenetically oriented complex therapy, allows for optimal adapted, adequate and individual organ-preserving therapy of intraocular melanoma.



Vertical axis: cumulative survival rate
 Horizontal axis: observation period in months.
 — Patients who underwent TTT + BT and IFT.
 -----Control group TTT + BT + IFT + SIAC (cisplatin)

Figure 4: Comparative analysis of survival of patients with UM who underwent TTT + BT + IFT + SIAC (cisplatin) and in the control group who underwent TTT, BT and IFT as organ-preserving treatment.

Conclusion

Conducting SIAC (cisplatin) in combination with TTT, BT and IFT in patients with UM increases the sensitivity of tumour cells to photodestruction and local radiotherapy, which promotes more active tumour regression.

Declaration of Conflict of Interest

The author does not have any real or potential conflict of interest (financial, personal, professional or other interests) that could affect the subject or material of this manuscript. I confirm that this paper is not being submitted simultaneously elsewhere.

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