

METHODS FOR COMBINATION TREATMENT OF METASTATIC UVEAL MELANOMA

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Uveal melanoma (UM) is a rare primary malignant tumor originating from uveal melanocytes (choroid (90%), ciliary body (6%), iris (4%)) of the eye. According to the aggregate data, the tumor incidence is 5.2 cases per 1 million population. In Russia this value varies between 6.23–8 cases per 1 million adult population across the regions. UM most often spreads to the liver (89–93%). The clinical case of using transarterial chemoembolization (carboplatin) in combination with immunotherapy (nivolumab + ipilimumab) in patients with metastatic liver disease from UM is provided. The disease control within 12 months has been achieved, which, in turn, demonstrates the possibility and efficacy of multidisciplinary approach.

Keywords: uveal melanoma, transarterial chemoembolization, immunotherapy, carboplatin, metastatic liver disease

Author contribution: Kolomiets KV — manuscript writing, editing; Ponomareva ES, Posypina YaR — manuscript writing, literature review, data analysis; Mihailov II, Mandzhiiev CB — manuscript writing, literature review, data acquisition; Bulgakov SM, Repunova VI — manuscript writing, literature review, concept and design; Povetkina EV, Tuguz RR — manuscript writing, literature review, manuscript revision.

Compliance with ethical standards: the patient submitted the informed consent to publication of the anonymized personal medical data.

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Received: 22.10.2023 **Accepted:** 29.11.2023 **Published online:** 22.12.2023

DOI: 10.24075/brsmu.2023.051

КОМБИНИРОВАННЫЕ МЕТОДЫ ЛЕЧЕНИЯ МЕТАСТАТИЧЕСКОЙ УВЕАЛЬНОЙ МЕЛАНОМЫ

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Уvealная меланомa (УМ) — редкая первичная злокачественная опухоль, формирующаяся из меланоцитов увеального тракта (хориоидеи (90%), цилиарного тела (6%), радужной оболочки (4%)) глазного яблока. По совокупным данным, уровень заболеваемости составляет 5,2 случая на 1 млн населения. В России этот показатель в разных регионах варьирует от 6,23 до 8 случаев на 1 млн взрослого населения. Наиболее часто (89–93%) УМ метастазирует в печень. Представлен клинический случай использования методики трансартериальной химиэмболизации (карбоплатин) в комбинации с иммунотерапией (ниволумаб + ипилимумаб) у пациента с метастатическим поражением печени увеальной меланомой. Был достигнут контроль заболевания на протяжении 12 месяцев, что, в свою очередь, демонстрирует возможность и эффективность мультидисциплинарного подхода.

Ключевые слова: увеальная меланомa, трансартериальная химиэмболизация, иммунотерапия, карбоплатин, метастатическое поражение печени

Вклад авторов: К. В. Коломиец — написание статьи, редактирование; Э. С. Пономарева, Я. Р. Посыпина — написание статьи, обзор литературы, анализ данных; И. И. Михайлов, Ч. Б. Манджиев — написание статьи, обзор литературы, сбор данных; С.М. Булгаков, В. И. Репунова — написание статьи, обзор литературы, концепция и дизайн; Е. В. Поветкина, Р. Р. Тугуз — написание статьи, обзор литературы, переработка статьи.

Соблюдение этических стандартов: пациент подписал добровольное информированное согласие на публикацию персональной медицинской информации в обезличенной форме.

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Статья получена: 22.10.2023 **Статья принята к печати:** 29.11.2023 **Опубликована онлайн:** 22.12.2023

DOI: 10.24075/vrgmu.2023.051

Uveal melanoma (UM) is a rare primary malignant tumor originating from uveal melanocytes (choroid (90%), ciliary body (6%), iris (4%)) of the eye. According to the aggregate data, the incidence level is 5.2 cases per 1 million population. In Russia this value varies between 6.23–8 cases per 1 million adult population across the regions. The average age at diagnosis is 62 years, while the peak age range is 70–79 years [1, 2]. However, despite the achievements in treatment of primary tumor and radical nature of surgery, the majority of patients develop distant metastases. Metastatic disease is found in less than 2% of patients when performing initial diagnosis of the eye tumor. Liver is the main target organ for metastasis in 89–93% of cases. Such tropism of UM toward hepatocytes is explained by the fact that there are three types of receptors hyperexpressed in the primary tumor on the cell surface: IGF-1R (insulin-like growth factor receptor), cMET (HGFR — hepatocyte growth factor receptor) and CXCR4 (chemokine receptor). Their main

function is to control cell migration, cancer cell invasion and proliferation [3, 4]. The median overall survival (OS) without surgery in this group of patients reaches 2–3 months.

Immunotherapy, transarterial chemoembolization (TACE), immunoembolization, radioembolization, thermal ablation, and isolated chemoperfusion are the methods most commonly used for treatment of metastatic liver disease from UM.

The use of TACE to control growth of metastatic liver melanoma was first reported in 1986. In 1986, the use of cisplatin and polyvinyl alcohol particles during chemoembolization to control growth of UM metastases in the liver was started [5].

To date, a total of 19 studies focused on TACE efficacy in patients with metastatic liver disease from UM have been published, among them 13 retrospective studies, five prospective studies, and one randomized study. The median overall survival (OS) varies between 5.2 and 23 months. Cisplatin was the most commonly used drug. Other chemotherapy agents were

as follows: vinblastine, dacarbazine, vincristine, dactinomycin, carmustine, mitomycin C, doxorubicin, irinotecan, paclitaxel, carboplatin, and melphalan [1, 2].

Despite the achievements in treatment of metastatic melanoma of the skin, UM still shows poor sensitivity to drug therapy, including advanced immunotherapy with immune checkpoint inhibitors, target therapy and chemotherapy. Nevertheless, despite lower efficacy of combination immunotherapy for UM relative to melanoma of the skin, its positive role was noted in the recent years. According to the data provided by different authors, despite the 1-year survival rate within 30–50%, the combination of ipilimumab and nivolumab is considered to be the most effective among all other treatment options showing low efficacy.

A retrospective analysis of the treatment outcomes of eight patients with metastatic UM was conducted in 2019. The patients received combination therapy with ipilimumab and nivolumab along with TACE followed by nivolumab maintenance therapy. In 5 patients with stage M1a disease out of 8, life expectancy of 12–24 months was achieved. Life expectancy of three patients with stage M1b disease was 7–30 months. Partial response was achieved in two patients, stabilization of disease in four patients; disease progression was observed in two patients. The median OS (time from the date of initial immunotherapy administration to the date of death/last follow-up) of eight patients calculated using the Kaplan–Meier method was 14.2 months [6, 7].

Assessment of lactate dehydrogenase (LDH) levels showed that the complete response rate of patients with LDH levels above normal was very low: complete response was observed in only one patient out of 105. LDH levels were excluded from the list of the complete response prognostic factors to be considered, when PD-L1 and tumor burden were taken into account. The latter, as is known, represents an important factor when considering the likelihood of positive response and long-term survival associated with the use of such drug, as pembrolizumab (antibody that inhibits PD-L1) [8].

The case study was aimed to demonstrate the possibility and efficacy of multidisciplinary approach: using TACE (carboplatin) in combination with immunotherapy in patient with metastatic liver disease from UM.

Clinical case

Patient P., 62 years old, contacted the clinic in February 2023. Ophthalmic examination performed in February 2019 revealed a left eye ciliochoroidal melanoma sized 13 x 14 mm on ultrasound. Given the neoplasm size and the lack of media transparency, eye removal surgery was recommended. Enucleation of the left eye was performed on July 7, 2020 at the City Emergency Hospital (Volgodonsk).

Findings of the surgical specimen histopathological examination, August 27, 2020: UM composed of nevus-like and spindle cells. Scleral tumor invasion in certain areas. Tumor containing large amounts of melanin. High mitotic count, vascular invasion.

Then the patient underwent scheduled follow-up examinations every 3 months, with which together with the two-fold increase in the interval between the last instrumental examinations (6 months) 17 month later a mass in the right lobe of the liver (S6–S7) up to 8 cm in diameter, which had not been seen before, was found after enucleation of the left eye. Two weeks later abdominal computed tomography (abdominal CT) revealed one more mass up to 1.5 cm in diameter in S8 of the liver. This suggests that it is reasonable to perform appropriate diagnostic imaging in all patients:

- Abdominal MRI (magnetic resonance imaging), August 21, 2020: MR features of diffuse changes in the pancreas;

- Laboratory tests, November 23, 2020 within the age norm, except for LDH level elevation to 458 U/L (reference range: 135–225 U/L).

November 18, 2020 — spiral CT (spiral computed tomography) of the abdomen and retroperitoneal space that revealed diffuse changes in the liver tissue and the pancreas, simple cyst on the right kidney;

- Laboratory tests, November 29, 2021 within the age norm, LDH 223.0 U/L, ESR (erythrocyte sedimentation rate) 48 mm.

Abdominal spiral CT, November 19, 2021: left adrenal mass sized 1.7 x 1.4 cm could be seen, probably due to adenoma.

abdominal MRI, November 18, 2021 — summary: diffuse changes in the pancreas, cyst on the right kidney, left adrenal adenoma;

- Laboratory tests, May 13, 2022 within the age norm, LDH 277.0 U/L, ESR 42 mm.

- Abdominal MRI, May 19, 2022: MR features of diffuse changes in the liver and pancreatic tissue. Left adrenal mass lesion (adenoma, incidentaloma).

Abdominal CT, November 25, 2022, summary: masses in the right lobe of the liver (not previously seen).

Contrast-enhanced abdominal CT, December 13, 2022: CT features of metastasis masses in the liver right lobe (S7–S6 — low density heterogeneous mass without clear margins sized 78 x 47 x 75 mm showing contrast uptake heterogeneity; S8 — low density lesion 14 mm in diameter (not previously seen) showing low contrast uptake).

Histological examination protocol of December 19, 2022, summary: liver fragment showing the presence of a solid tumor with necrotic foci consisting of atypical epithelioid cells with hyperchromatic nuclei and eosinophilic cytoplasm without clear margins; some cells contained the pigment melanin. Liver trephine biopsy showed metastatic melanoma.

The following diagnosis was established: secondary liver cancer; stage III A T3bN0M0 left eye uveal melanoma, postoperative condition (July 2020), progression (November 2022), (HEP), clinical group 2.

Status localis on ophthalmic examination: left-sided anophthalmos, recurrent herpes simplex keratitis (epithelial corneal dystrophy), immature mixed senile cataract, pigmented choroidal nevus in the right eye.

During the scheduled chemotherapist consultation (December 29, 2022) it was recommended to prescribe the following immunotherapy (IT) regimen in case of satisfactory blood cell counts and no somatic contraindications considering the disease dynamics: nivolumab 3 mg/kg on day 1 + ipilimumab 1 mg/kg on day 1; 21 day cycle.

The patient contacted the clinic of the Rostov State Medical University after one course of IT, in February 2023. Given liver involvement, medical history and instrumental assessment data, as well as tumor expansion, it was decided to perform transarterial chemoembolization (TACE) on the case conference.

Surgical intervention specifications, February 24, 2023: the right radial artery puncture using the common site was performed in the supine patient in aseptic environment of the cath lab after the appropriate surgical site conditioning (18G angiographic needle). The Seldinger technique of catheter placement was used (5F introducer, 11 cm). A 5F HH1 catheter (125 cm) was sequentially introduced into the right brachial artery, axillary artery, brachiocephalic trunk, aortic arch, thoracic aorta through the O35" hydrophilic sheath (180 cm). Sheath was removed, and aortography was performed: the celiac

trunk arised at the level of the L1 vertebral body. Selective catheterization of the celiac trunk orifice was performed: cranial approach, non-dilated and tortuous splenic artery, no hypertrophy of gastric branches (anastomoses). The common hepatic artery arised from the celiac trunk in a normal way, division into the left and right hepatic arteries, gastroduodenal artery were normal. The catheter sheath was replaced. The right hepatic artery supplying the tumor foci was selectively catheterized using the H1 catheter (125 cm) with the 0.014" Asahi Chikai microsheat (ASAHI INTECC CO., LTD; Japan) (165 cm). TACE of the arteries supplying the foci was performed (lipiodol 20 mL + carboplatin 450 mg). Artery embolization was performed using the Cutanplast hemostatic sponge (Mascia Brunelli; Italy). The follow-up angiography revealed a prominent contrast uptake reduction along the right hepatic artery segmental branches supplying the tumor foci. No signs of nontarget embolization were revealed. Catheter was inserted into the aorta; the follow-up angiography showed that the right and left hepatic, gastroduodenal, superior mesenteric arteries were not compromised. The instruments were sequentially removed. Introducer was removed, compression hemostasis was provided (8 min, stable, aseptic pressure dressing).

To prevent thromboembolic complications, supportive drug therapy was prescribed after surgery that included anticoagulants and nonsteroidal anti-inflammatory drugs as analgesics, since post-embolization syndrome (PES) with the duration between two days and three weeks was observed in many patients (90–100%) after TACE. It is believed that PES is mediated by inflammatory cytokines released due to liver necrosis caused by embolization or chemotherapy drugs. The major PES manifestations are as follows: fever, pain in the right hypochondriac/epigastric region, nausea, vomiting, liver failure worsening and, as a result, transaminase level increase. However, fortunately, PES can be successfully relieved by symptomatic drug therapy.

The patient was discharged on day 8 after surgery; at the time of discharge he considered his condition to be satisfactory despite the size of metastatic foci; a low-grade fever was reported within three days after TACE, along with moderate pain in the right hypochondriac and epigastric regions.

Then the patient underwent IT courses (3 courses) at the place of residence, and the follow-up examination revealed improvement.

The contrast-enhanced abdominal CT performed on April 24, 2023, revealed CT features of metastasis masses in the liver right lobe (S7–S6 — low density heterogeneous mass without clear margins sized 54 × 43 × 61 mm showing contrast uptake heterogeneity; S8 – low density lesion 9 mm in diameter showing low contrast uptake). Comparison with the abdominal CT scan of November 25, 2022 revealed improvement. The TACE efficacy was assessed one month later based on CT/MRI with intravenous contrast using the RECIST 1.1 (2009) (Response evaluation criteria in solid tumours) criteria, according to which partial response (regression) was achieved: > 30% sum of the largest sizes (long axes) of lesions.

On May 14, 2023 (3 months later), the patient was admitted again for the second TACE procedure, because of the previously achieved partial response to combination therapy. He underwent four IT courses. Given liver involvement, expansion and improvement, TACE was performed: lipiodol 20 mL + carboplatin 450 mg. Artery embolization was performed using the Cutanplast hemostatic sponge. Supportive drug therapy was prescribed after surgery. The patient was discharged on day 7 after surgery; at the time of discharge he considered his condition to be satisfactory and reported no fever or subcostal pain.

According to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), in which the adverse event severity varies between 0 (normal range) and 4 and 5 (disability and death, respectively), grade 1 fever was observed. Furthermore, after TACE, moderate pain in the right hypochondriac and epigastric regions (grade 1) was reported during the early postoperative period.

To date, the follow-up period is 12 month with no signs of disease progression. The patient's condition is satisfactory. He leads an active life and undergoes the courses of systemic IT since June 2023 until now (November 2023) according to the maintenance phase regimen: nivolumab 3 mg/kg by intravenous infusion once every 14 days.

Clinical case discussion

TACE for UM liver metastases using carboplatin and lipiodol, viscous ethiodized oil that is selectively delivered through a catheter to induce ischemic tumor necrosis by blocking arterial inflow into the tumor (while healthy liver parenchyma is preserved due to dual blood supply from the portal vein and hepatic artery), in combination with the gradual release of chemotherapy agent in the area of metastasis and its selective cytostatic effect with minimal systemic side effects. It is obvious that more than 70% patients with malignant hepatic tumors require palliative chemotherapy. However, systemic chemotherapy efficacy in inoperable cancer does not exceed 20–30% with survival of 3–4 months even in case of using several drugs. Apparently, when the chemotherapy drugs are administered intravenously, the therapeutic concentration is achieved only for a short while and does not have a necessary effect on the tumor cells, while prominent impairment of the liver detoxication function limits the use of high anticancer drug doses. Immunotherapy significantly improved the prognosis of patients with melanoma of the skin, but no such clinical effect is observed in patients with metastatic UM. However, the efficacy of combination immunotherapy is higher than that of other drug treatment options (anti-PD-1 monotherapy, chemotherapy, etc.) used for UM. Partial hepatectomy can be considered in patients with good liver function only, to avoid potential decompensation of liver function. Systemic chemotherapy is also of limited use in patients with unresectable liver metastases. That is why alternative treatment methods, such as radiofrequency ablation and microwave ablation, are recommended for such patients. When neither surgery, nor local ablation techniques succeed, TACE is an option for local tumor control. This treatment gave promising results in patients with inoperable liver metastases. Due to the combination of direct chemotherapeutic use and a vascular occlusion technique, cytostatic substances are in contact with the target malignant cells over a longer time.

One of the TACE shortcomings is represented by formation of hypoxic microenvironment that enhances neoangiogenesis and can thereby contribute to early progression. It is well known that angiogenesis is a key factor of tumor growth and metastasis in many cancer types, including metastatic liver cancer [9].

CONCLUSION

The features of the UM clinical course compared to the skin form of the disease include longer time to progression and predominance of liver metastasis; molecular genetic features are also different (the major molecular abnormalities typical for melanoma of the skin (BRAF, NRAS mutations) are not involved in induction of the disease processes associated with UM).

Based on the available data, the combined use of ipilimumab and nivolumab represents one of the main treatment regimens for this group of patients. The new combination treatment methods involving TACE and immunotherapy (nivolumab + ipilimumab in the reported case study) used to treat metastatic liver disease from UM made it possible to control the disease course throughout 12 months. The patient demonstrated improvement in the form of reduced metastatic foci size, which was nevertheless encouraging, since minimal median OS of this category of patients associated with TACE and no surgical treatment was exceeded by 2 and 4 times, respectively. However, further research is needed to determine optimal therapy in order to achieve maximum efficacy and minimize side effects.

Prospective randomized studies will help determine safety and efficacy of the combination locoregional and systemic therapy for metastatic UM. TACE is an alternative treatment method for patients with unresectable liver metastases allowing for selective delivery of high chemotherapy agent doses to the tumor bed and embolize the target vessels with minimum systemic bioavailability, which minimizes systemic side effects, thereby preserving the surrounding liver tissue. The lack of effective treatment methods for metastatic liver disease from UM forces us to seek for new approaches to treatment of this disorder. In this regard, today, it is necessary to optimize treatment based on the available methods, such as systemic (chemotherapy/immunotherapy) and local (TACE and other) methods.

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