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MODERN APPROACHES TO IMMUNOTHERAPY OF METASTATIC UVEAL MELANOMA. REVIEW

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ABSTRACT

Uveal melanoma is a tumor of neuroectodermal origin, developing from melanocytes of the uveal tract (choroid, ciliary body, and iris). This disease is a rare type of melanoma, which accounts for about 3% of all reported cases of melanoma. Uveal melanoma differs from skin melanoma and mucosal melanoma in both clinical course and molecular genetic properties. For uveal melanoma, the search for new targets of targeted antitumor therapy is actively underway. A promising area of treatment for metastatic uveal melanoma is immunotherapy with immunological response regulators (anti-PD-1 and anti-PD-L1 monoclonal antibodies) and antitumor vaccines. Selumetinib did not show any advantages in overall survival, however, it became the first targeted drug with proven clinical efficacy in metastatic uveal melanoma. The study of the fundamental mechanisms and the search for predictors of antitumor immune response in uveal melanoma are necessary for the development of new, more effective methods of immunotherapy for metastatic uveal melanoma.

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Introduction

Uveal melanoma is a malignant tumor of neuroectodermal origin, the incidence of which ranges from four to ten cases per 1 million. Uveal melanoma accounts for only 3% of all melanomas [1]. About 90% of uveal melanomas are localized in the choroid, 6% – in the ciliary body, and 4% – in the iris [2]. Half of the patients develop metastatic disease regardless of the choice of treatment for the primary tumor in the eye [3]. The factors of unfavorable prognosis in uveal melanoma include the age of patients, the size of the primary tumor, cellular composition (mixed-cell or epithelioid melanoma), extraocular growth, chromosomal changes (monosomy of the 3rd and/or amplification of the 8th chromosome) [4]. Due to the absence of lymphatic vessels in the eye, uveal melanoma metastasizes hematogenically, more often to the liver (up to 90%), lungs (25%), bones (15%), and skin (10%). The median life expectancy for liver metastases in patients with uveal melanoma is about nine months [5]. The median life expectancy in the group of patients with extrahepatic manifestations of the disease, according to various authors, ranges from 19 to 28 months [6].

Uveal melanoma differs from skin melanoma and mucosal melanoma both in its clinical course (late metastasis with predominant liver damage) and in its molecular genetic properties (low frequency of mutations in the BRAF, NRAS, and cKIT genes). Uveal melanoma is characterized by activating somatic mutations in the GNAQ and GNA11 genes [7].

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The low effectiveness of standard chemotherapy explains the unfavorable prognosis in patients with metastatic uveal melanoma [8]. This requires a constant search for effective methods of treatment.

New Directions in the Treatment of Metastatic Uveal Melanoma

By analogy with metastatic melanoma of the skin, in the therapy of which BRAF/MEK kinase inhibitors have already demonstrated an increase in overall survival, the effectiveness of systemic therapy with drugs from these groups is also evaluated in metastatic uveal melanoma. However, until recently, no drug has shown a significant effect on overall and relapse-free survival in metastatic uveal melanoma. The situation changed in 2013 when the results of phase II clinical trials were published to evaluate the effectiveness of the MEC–selumetinib inhibitor in patients with metastatic uveal melanoma with mutations in the GNAQ and GNA11 genes. For the first time, Selumetinib has demonstrated efficacy in increasing the time to progression compared to standard chemotherapy with temozolomide. The median time to progression in the selumetinib group was four months whereas in the temozolomide group, it was a month [9, 10]. Selumetinib did not show any advantages in overall survival, but despite this, it became the first targeted drug with proven clinical efficacy in metastatic UVEAL melanoma and passed accelerated FDA registration (Food and Drug Administration – FDA).

The active study of new MEK inhibitors continues. However, according to the latest data, their effectiveness is still low [11].

Immune Response Blockers for the Treatment of Metastatic Uveal Melanoma

Simultaneously with the effectiveness of targeted chemotherapy, the efficacy of anti-CTLA-4- and anti-PD1-/PD-L-monoclonal antibodies in metastatic uveal melanoma is being actively studied in clinical studies. Preliminary data from a clinical study conducted based on four clinics in the USA and Europe on the use of the anti-CTLA-4-monoclonal antibody ipilimumab in metastatic uveal melanoma seemed encouraging. The study involved 34 patients with metastatic uveal melanoma. The researchers evaluated the efficacy and toxicity of ipilimumab at a dose of 3 mg/kg. By the 12th week of therapy, 46% of patients had stabilization of the disease. However, larger studies have not shown significant benefits of ipilimumab in the treatment of metastatic uveal melanoma [12, 13]. The characteristics of patients who received anti-CTLA-4 immunotherapy (ipilimumab) are presented in **Table 1**.

Table 1. Characteristics of patients who received anti-CTLA-4 immunotherapy (ipilimumab)

General group (n = 10)	Age, years	Localization of the primary tumor	Time to progression after the initial diagnosis, months	Localization of the metastatic process	General condition: ECOG status	The first line of therapy
1	63	choroid	69.76	liver	0	Polychemotherapy
2	68	choroid	16.73	liver	1	Polychemotherapy
3	57	choroid	144.62	liver	0	Polychemotherapy
4	46	choroid	23.80	liver	0	Polychemotherapy
5	38	choroid	196.37	liver + other	1	Polychemotherapy
6	49	choroid	115.82	organs	1	Polychemotherapy
7	43	ciliary body	59.84	liver + other	0	Polychemotherapy
8	28	choroid	120.72	lungs	0	Polychemotherapy
9	61	choroid	186.71	liver	0	Chemoembolization
10	53	choroid	8.78	liver	1	Ipilimumab

Our own clinical experience also indicates the low effectiveness of ipilimumab in the treatment of metastatic uveal melanoma. About 160 patients with metastatic melanoma were treated under the extended access program. Ten of them have metastatic uveal melanoma. The age of the patients ranged from 28 to 68 years, the sex ratio (m:w) was 1:1, and the ECOG status was 0 or 1. On average, all patients received four injections of ipilimumab at a dose of 3 mg/kg. The median progression-free life expectancy was 3.47 months. Against the background of therapy, not a single partial and complete response was registered. One patient had a long-term stabilization of the disease.

Other drugs from the group of immune response blockers for the treatment of patients with metastatic uveal melanoma are anti-PD-1-monoclonal antibodies (nivolumab, pembrolizumab).

In a study by L.A. Kottschade *et al*. pembrolizumab therapy was received by seven patients with metastatic uveal melanoma (all patients had previously had disease progression during ipilimumab therapy). The average age of patients at the time of inclusion in the study was 64.5 years, ECOG status of 0 or 1. Patients received pembrolizumab at a dose of 2 mg/kg once every three weeks until the disease progressed or intolerable toxicity. The median progression-free life expectancy was 12.2 weeks

(in the range of 3.14-41), and two patients were receiving therapy by the time the data were published (February 2015). One complete and one partial response was registered against the background of therapy. Stabilization of the disease was recorded in one patient [14].
The results of this pilot clinical trial served as a justification for a larger study of pembrolizumab in metastatic uveal melanoma [15]. According to the data presented at ASCO-2016, pembrolizumab has not shown clinical efficacy in the treatment of metastatic uveal melanoma.
Our own experience of using anti-PD-L drugs is limited to one observation. Patient 1(50-year-old, female) with metastatic uveal melanoma received 136 mg of pembrolizumab in the first line. In total, six injections were carried out at the indicated dose. The results of the examination showed the progression of the disease. In this regard, treatment with pembrolizumab was discontinued, and the patient continued to receive standard chemotherapy as part of the second line.

Vaccination of Metastatic Uveal Melanoma
Vaccine therapy remains one of the promising areas of melanoma immunotherapy. According to preliminary data, in patients who received the vaccine, the median total life expectancy reached 19.2 months, which is comparable to the effectiveness of local treatment methods, namely radical surgical removal of solitary metastases of uveal melanoma in the liver. At the same time, a tumor-specific immune response was recorded in four out of 14 patients with metastatic uveal melanoma [16].

Clinical Cases
Let's consider two clinical cases of vaccination of patients with choroid melanoma with multiple liver metastases. The vaccine was administered in a dose range from 5 to 40 million cells intradermally every two weeks. The patients were monitored for three months after the end of the vaccine administration. The safety of the vaccine was judged by early (first – third day) and delayed adverse reactions on the toxicity scale (criteria of STS v 3.0). In particular, the presence of a local irritant effect, pyrogenicity, immunotoxicity, and other clinical manifestations of toxicity (hematological, biochemical, cardiac activity indicators, etc.) was evaluated. The response to treatment was recorded separately.
Patient 2 (female) was vaccinated 32 times. The dynamics of the immunological indicators are presented in **Figure 1**. As we can see, the expression of CD25 activation antigen varies within limited limits corresponding to the norm. The number of cells secreting interferon-gamma increases slowly and insignificantly. There is an increase in cells (CD16 and CD8) secreting granzyme B. Against the background of vaccination, this patient recorded stabilization of the disease for five months. Among the side effects, there was a slight weakness on the first or third day of vaccination and a local area of hyperemia (d = 0.2–1.0 cm).
Patient 3 (female) underwent 25 vaccinations. The dynamics of the expression of the CD25 activation marker are shown in **Figures 2 and 3**. The expression of the CD25+ activation marker (interleukin receptor) increased to 8.4% by the 12th vaccination. Among the cells expressing granzyme B, the number of CD8+ cells ranges from 4.8 to 6.6%, and the number of CD16+ cells decreases to 8.7. According to the control study, the stabilization of the process was recorded for six months. No side effects were reported.

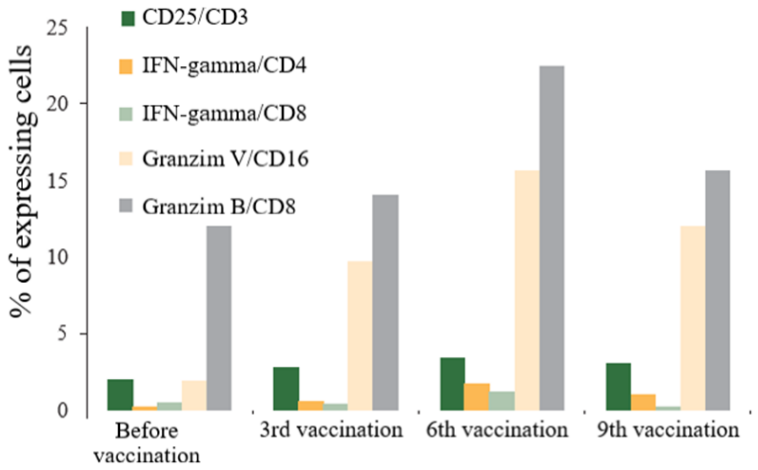


Figure 1. Dynamics of immunological parameters of Patient 2

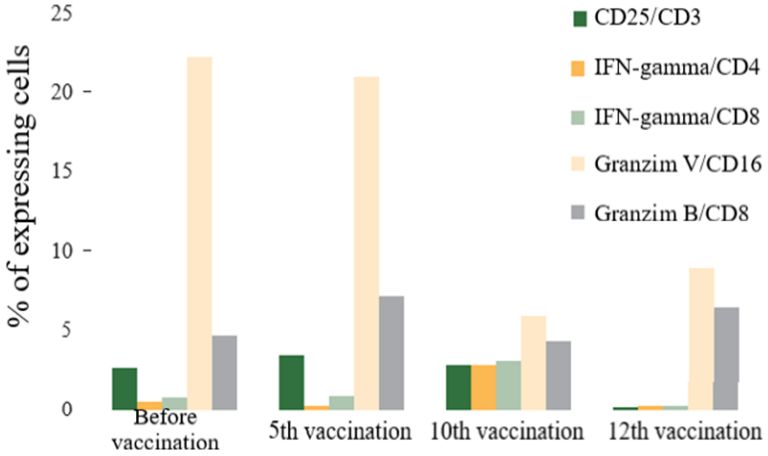
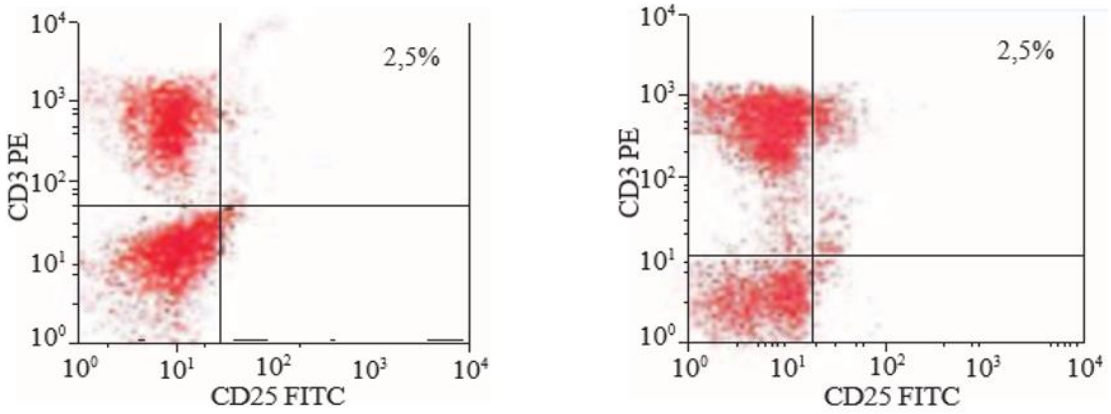


Figure 2. Dynamics of immunological parameters of Patient 3

A factor that allows us to judge the relationship between immunological mechanisms and the mechanism of inhibition of the tumor process under the action of the Allogen vaccine is the positive dynamics of activating granzyme B molecules on CD16 cells, the expression of CD25 and interferon-gamma on CD4/CD8 cells against the background of stabilization in patients with progressive disease.



a) b)

Figure 3. CD3+CD25+ T-lymphocyte expression during Allogeneic vaccine administration in patient 3 (a) number of cells before vaccination, b) number of cells at the 12th vaccination)

Conclusion

A review of the literature and our clinical data indicate the lack of clinical efficacy of immunotherapeutic approaches to the treatment of metastatic UVEAL melanoma. Nevertheless, the study of the fundamental mechanisms and the search for predictors of antitumor immune response in uveal melanoma are necessary for the development of new, more effective methods of immunotherapy for metastatic uveal melanoma.

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Ethics statement: All patients signed volunteer agreement for participation in the experiment.

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