Immunotherapy for uveal melanoma

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Practice points

- Uveal melanoma (UM) is the most common primary intraocular cancer and the second most common type of primary melanoma.
- The liver is the most common site of metastasis, and the only site of metastasis in many patients with UM.
- While local treatment of primary UM is quite effective, there are no systemic therapies to improve survival in patients with metastatic UM.
- UM has a unique immunological aspect and interacts with the tumor environment of the eye and the liver.
- Adjuvant immunotherapeutic approaches using Bacillus Calmette–Guérin and low-dose interferon failed to show clinical benefit.
- In contrast to cutaneous melanoma, the clinical activity of immune checkpoint inhibitors such as ipilimumab and pembrolizumab is limited in metastatic UM.

Uveal melanoma (UM) is a rare cancer with a high mortality rate. In comparison to cutaneous melanoma, UM has unique immunological features. Arising in the immune suppressive environment of the eye, it maintains immune resistance once metastatic. This is considered a major obstacle for successful immunotherapy in UM. However, a growing body of evidence suggests strategies that may abrogate resistance and enhance antitumor immunity in UM. Recently, three new immune agents have been approved for melanoma. While these drugs demonstrate durable clinical responses with long-term remissions in metastatic cutaneous melanoma, only limited data exist in metastatic UM. In this review, immunological aspects of UM and data from clinical studies of immunotherapeutic agents and regimens for UM will be discussed.

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Background

Uveal melanoma (UM) arises from melanocytes in the uveal tract of the eye and is the most common primary intraocular cancer in adults as well as the second most common type of primary melanoma following cutaneous melanoma. Although both cutaneous melanoma and UM arise from melanocytes derived from neural crest cells, UM has unique characteristics. While cutaneous melanomas spread via lymphatics, UMs metastasize hematogenously with rare exception [1]. Interestingly, the

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liver is the most common site of metastasis in patients (up to 95%) with metastatic UM [2]. Several *in vitro* studies suggested c-MET, IGF-IR and CXCR-4 as possible mechanisms of liver predominant metastasis in UM [3]. However, none of them were confirmed clinically. Once metastasis develops, the prognosis of metastatic UM is quite dismal. The median survival from diagnosis of metastasis is less than 6 months with the death rate of 80% at 1 year after diagnosis of metastatic disease [4].

While local treatment of the eye such as brachytherapy, proton beam radiation and enucleation is effective with low local recurrence rate, treatment of metastatic disease is quite challenging and no systemic therapy has been shown to improve survival [5]. Therefore, new effective therapeutic approaches for metastatic UM are needed.

The advancement of cancer immunology and the discovery of immune checkpoints have led to the development of effective immunotherapy such as ipilimumab, nivolumab and pembrolizumab for patients with advanced cutaneous melanoma. However, the efficacy of the immunotherapy has not been well described in UM likely due to exclusion of UM in most of those clinical trials. It has been believed that immune surveillance in UM may not be as effective as cutaneous melanoma since UM takes advantage of an immune suppressive ocular microenvironment in primary sites, UM adopts the mechanisms of ocular immune privilege to abrogate antitumor immunity in metastatic sites, and the main metastatic sites of UM is the liver which is considered as an immune privileged organ. However, there is a growing body of evidence that immunotherapeutic approaches may elicit antitumor immunity to attenuate disease progression and improve clinical outcome in UM. Currently, immunotherapeutic approach has been of great interest in UM due to poor prognosis of metastatic UM with very limited systemic treatment options. In this paper, we will review immunological aspects of UM and summarized data from clinical studies of immunotherapy for UM.

Immunobiology of the eye & UM

Due to the limited capacity for regeneration of ocular cells, excessive inflammatory responses with collateral damage of the eye may lead to permanent blindness. To protect the eye from vision-destroying inflammation, the eye has a

unique immune suppressive environment which is called immune privilege. Multiple factors including physical barriers, soluble and membrane bound molecules, and immune suppressive cells contribute to immune privilege of the eye. Intraocular inoculation of highly immunogenic tumor cells can induce progressive growth of the tumor in the eye [6], which suggests ocular immune privilege can be hijacked by UM to escape immune surveillance in the primary site. UM also adopts the mechanisms of ocular immune privilege to evade antitumor immunity in distant metastatic sites.

Anatomically, lack of lymphatics and blood vessels in the cornea [7,8], and tight junctions of vascular endothelial cells (blood–ocular barrier) in the iris and retinal vessel [9] limit immune responses in the eye and primary UM. However, the unique anatomy of the eye does not completely prevent immune responses. Previous data demonstrated peptide specific T-cell expansion following immunization in the eye [10], lymphatic drainage in the ciliary body of the uveal tract [11], lymphangiogenesis in corneal transplant rejection [8] and lymphangiogenesis in ciliary body UM [12,13]. Thus, the unique anatomical barriers of the eye can raise the threshold for immune responses in the eye, which may be permissive for the growth of UM by escaping immune surveillance.

Multiple inhibitory cell surface molecules which inhibit T-cell function are expressed on ocular cells and UM. PD-L1 which induces T-cell exhaustion and deletion by binding to PD-1 on activated T cells is expressed constitutively in cornea, iris, ciliary body and retina, and it plays a critical role in corneal allograft survival by apoptosis of infiltrated effector T cells [14]. Upregulation of PD-L1 expression on primary and metastatic UM by treatment of interferon- γ has been reported to promote immune escape by impairing effector T-cell function [15]. To prevent autoimmune disease and minimize collateral damage, activated T cells express Fas, and its ligation with FasL induces apoptosis of activated T cells for immune homeostasis, a process known as activation-induced cell death [16]. Ocular cells take advantage of activation-induced cell death for immune privilege. Expression of FasL on ocular tissues plays a crucial role in corneal allograft survival by apoptosis of effector T cells [17]. In addition to direct FasL expression on UM [18], UM secretes soluble FasL to inhibit cytotoxic T-cell mediated tumor lysis [19]. The expression

of inhibitory molecules such as PD-L1 and FasL on both ocular cells and UM may contribute to tumor development and progression by suppression of antitumor immunity.

The ocular microenvironment is enriched with immune suppressive soluble factors such as TGF- β , α -melanocyte-stimulating hormone (α -MSH), calcitonin gene-related peptide, macrophage migration inhibitory factor (MIF), somatostatin, VIP and VEGF [20]. TGF- β is a well-known immunosuppressive cytokine and has direct and indirect immune suppressive effect by inhibiting natural killer (NK) cell mediated cytotoxicity [21], suppressing CD8 cytotoxic T-cell function, expanding Tregs and enhancing the function of Tregs [22,23]. α -MSH inhibits effector T cells by suppressing secretion of IFN- γ and inducing Tregs [24,25]. MIF deters NK cell mediated killing [21]. Both α -MSH and calcitonin gene-related peptide inhibit endotoxin-induced inflammatory activity by suppressing nitric oxide production of macrophages and induce an anti-inflammatory cytokine production by macrophages [25,26]. Somatostatin and VIP also contribute to the ocular immunosuppressive microenvironment by suppressing IFN- γ production by activated T cells [27,28]. VEGF, a potent angiogenic factor suppresses antitumor immunity by inhibition of dendritic cell maturation and T cell response [29]. Recent data have demonstrated that baseline VEGF level is correlated with poor clinical response to immunotherapy such as high dose IL-2 and ipilimumab [30,31]. The aqueous humor and vitreous fluid from eyes with UM contains increased level of immune suppressive cytokines including MIF, VEGF and CCL2 which attracts tumor-promoting macrophages in comparison to control eyes without UM [32–34]. UM also secretes IL-10 [35], VEGF [36], TGF- β [37] and MIF [38] to create immune suppressive environment by inhibiting NK cell mediated cytotoxicity and CD8 cytotoxic T-cell function in primary and metastatic sites. In addition, coculture of UM cells with activated T cells upregulates several chemokines including CXCL8, CCL2, CCL5 and VEGF, which may lead to migration of tumor promoting macrophages and/or differentiation into tumor promoting macrophages [39]. Several retrospective studies demonstrated that the density of macrophages correlated with the density of blood vessels and metastatic mortality in UM [40,41], suggesting macrophages may promote tumor angiogenesis and tumor progression in UM.

Downregulation of HLA class I expression is one of the mechanisms to escape from immune surveillance in tumor. However, complete loss of HLA class I expression induces activation of NK cells and renders tumor cells more susceptible to NK cell mediated killing. In UM, NK cells are considered as one of the main mechanisms of immune surveillance. Lack of HLA class I expression correlates with improved overall survival [42]. Metastatic UM cells demonstrated complete loss of the ligand for the NK cell activating receptor, NKG2D [43], a tenfold higher expression of HLA class I than primary UM [44] and production of twice as much MIF as primary UM to escape from NK cell mediated cytotoxicity in the liver which is enriched in NK cells [45].

The predominant metastatic site of UM is the liver which is also considered as an immune privileged organ. In comparison to other organs, HLA matching does not change the outcome of liver transplantation and the rejection of transplanted liver is frequently impaired [46]. In addition, a liver allograft can induce protection on other allografts such as a kidney graft from the same donor [47], which suggests the role of liver in systemic immunosuppression. Although there are no data demonstrating liver tolerance inhibits antitumor immunity against metastatic UM, and clinical activity of immune therapeutic agents such as anti-CTLA-4 and anti-PD-1 antibodies has been observed in cutaneous melanoma patients with metastatic liver disease, metastatic UM may utilize immune privilege of the liver to escape from antitumor immunity.

Primary and metastatic UM stimulated with IFN- γ and ocular cells produce indoleamine 2, 3 dioxygenase (IDO) [48,49] which suppresses effector T-cell function by catabolizing the essential amino acid, tryptophan for T-cell proliferation [50]. Interestingly, it has been reported that IDO is a critical resistance mechanism of ipilimumab, and inhibition of IDO augments effectiveness of immunotherapy such as CTLA-4 blockade and PD-1/PD-L1 blockade in a preclinical study [51].

The eye can control systemic immune responses by the downregulation of systemic cell-mediated immune responses which is called anterior chamber-associated immune deviation (ACAID). ACAID also inhibits antitumor immunity against UM [52]. Although the exact mechanism of ACAID is unknown, it is believed that ocular F4/80+ antigen presenting

cells migrate to spleen and interact with T cells, NK T cells and B cells in the marginal zone of the spleen to induce antigen specific Tregs which suppress antigen specific systemic immune response [53,54].

Immunotherapy

Although UM hijacks the ocular immune privilege and creates an immune suppressive environment to escape antitumor immunity in primary and metastatic sites, there is considerable evidence that immune surveillance is still active, and immunotherapy may inhibit tumor progression in UM. Spontaneous regression of UM has been reported [55–57], which suggests active immune surveillance of UM although it is quite rare compared with cutaneous melanoma. Tumor-infiltrating lymphocyte (TIL) as well as high expression of tumor antigens including gp100, MAGE, MART-1 and TRP1 was found in primary and metastatic UM [58–60]. The direct and indirect evidence of active antitumor immunity rationalizes immunotherapeutic approaches in this disease.

Adjuvant immunotherapy

Adjuvant treatment for the prevention of metastatic disease in UM is attractive since 50% of UMs develop metastatic disease, and systemic treatment options for metastatic UM are very limited. Several clinical and molecular factors have been studied to identify high-risk UM developing metastatic disease. Tumor size, tumor location, age, extraocular extension, chromosomal aberrations and gene expression profiling have been reported to be associated with high risk of developing metastatic disease [61]. Among these factors, monosomy 3 and class 2 gene-expression profile are commonly used as molecular markers of high-risk UM, clinically. Monosomy 3 is a common cytogenetic event in 50% of UM [62], and it confers poor prognosis with a 3-year probability of metastasis up to 50% [63,64]. Class 2 gene-expression profile has been identified by gene-expression microarray analysis [65]. While UMs with class 1 signature have an extremely low risk of metastatic disease, those with class 2 have a very high rate of metastasis.

Although multiple adjuvant clinical trials have been conducted to prevent metastatic disease in the high-risk group, there are no studies to demonstrate improvement of distant metastasis-free survival or overall survival. Previously, a

randomized controlled clinical trial of methanol-extracted residue of *Bacillus Calmette–Guérin* (BCG) adjuvant treatment of posterior UM was undertaken [66]. In the study, 113 patients were randomly assigned to receive intradermal BCG ($n = 34$) or no treatment ($n = 79$), and no survival benefit was observed in adjuvant BCG-treated group (Table 1). Since adjuvant high dose interferon immunotherapy was approved for high-risk cutaneous melanoma in 1995, interferon has been evaluated for UM in adjuvant setting. In one study, 39 patients with UM received 3 million units of interferon three-times a week for 1 year, and survival was compared with a historical control group matched for sex, tumor location, largest tumor diameter and tumor height [67]. In another interferon study, 121 UM patients with the presence of at least one of the following characteristics: age ≥ 65 years, largest tumor diameter ≥ 15 mm, ciliary body involvement or extrascleral tumor extension were treated with 3 million units three-times a week for 2 years [68]. To evaluate the efficacy of the interferon in the study, historical controls matched for age, largest tumor diameter, gender and time between primary therapy and treatment initiation were selected. In both interferon studies, low-dose adjuvant interferon failed to demonstrate overall survival benefit in comparison to historical controls (Table 1). There are several completed clinical trials of adjuvant immunotherapy for high-risk UM patients (Table 2):

- Dacarbazine plus interferon for monosomy 3 patients (NCT01100528);
- Ipilimumab for high risk UM patients with class 2 gene expression, monosomy 3 or apical thickness ≥ 8 mm (NCT01585194);
- mRNA transfected dendritic cell vaccination for patients with monosomy 3 and HLA-A2 (NCT00929019); and
- Ongoing study, dendritic cells plus autologous tumor RNA for monosomy 3 patients (NCT01983748).

Local immunotherapy

• Liver directed immunotherapy

Since the liver is the predominant site of metastasis in most patients with UM, liver directed local treatments including surgical resection, hepatic artery embolization, hepatic artery infusion of

Table 1. Historic adjuvant immunotherapy trials.

Drug	Study design	n	Eligibility	Result	Ref.
BCG i.d. weekly for 4 weeks then monthly for 11 months	Randomized	113 (observation: n = 79; treatment: n = 34)	Posterior uveal melanoma	No difference in overall survival; p = 0.6	[66]
IFN- α , 3×10^6 IU, sc., three-times/week for 1 year	Nonrandomized	39	No evidence of metastatic disease, less than 2 months after primary treatment	No difference in 3-year survival rate compared with historical control; p = 0.27	[67]
IFN- α , 3×10^6 IU, sc., three-times/week for 2 years	Nonrandomized	121	Age ≥ 65 years, LTD ≥ 15 mm, ciliary body involvement or extrascleral tumor extension	No difference in 5-year melanoma related death rate compared with historical control; p = 0.91	[68]

BCG: Bacillus Calmette–Guérin; i.d.: Intradermally; IU: International units; LTD: Largest tumor diameter; sc.: Subcutaneously.

chemotherapy and radiofrequency ablation have been utilized in patients with metastatic UM. Immunoembolization with GM-CSF in metastatic UM was investigated in a Phase I study with hypothesis to increase local recruitment and maturation of dendritic cells to the tumor bed after ischemic necrosis by embolization [69]. Among 31 evaluable patients treated with immunoembolization in the study, a 33% objective response was reported. However, a subsequent Phase II study demonstrated significantly shorter median PFS in patients who received immunoembolization than control (3.7 vs 7.2 months; p = 0.01) with no survival benefit [70,71]. Currently, a Phase I study of radioembolization combined with ipilimumab (NCT01730157) is underway in patients with metastatic UM.

Systemic immunotherapy

• Chemoimmunotherapy

The nitrosourea, fotemustine, has a high hepatic extraction rate, which makes it an ideal agent to target liver metastases and response in extrahepatic metastatic disease has been reported. The activity of systemic or intrahepatic fotemustine with biotherapy including IL-2 and IFN- α -2b was evaluated in a Phase II, prospective study

of 48 patients with metastatic UM not amenable to resection (not including CNS). Patients were given fotemustine 100 mg/m² via hepatic artery infusion (if metastatic involvement solely hepatic) or via peripheral intravenous (iv.) infusion on day 1, and repeated on day 8 of the induction phase. Subcutaneous IL-2 at 10×10^6 IU/m² twice daily for 3 days was added on day 31. On days 36, 38 and 40, patients received IL-2 5×10^6 IU/m² and IFN- α -2b 10×10^6 IU/m². The subsequent cycle's fotemustine dose was given 3 days later (day 43). Assessment of activity was completed 3 months after initiating therapy, and resulted in one patient (2%) achieving complete response (CR) and six patients (12.5%) with partial response (PR) – for an overall response rate of 14.5% (95% CI: 6.1–28.4). An additional 18 patients (37.5%) had what was determined to be stable disease, and a median progression-free survival (PFS) of almost 1 year (range: 155–855 days). The median survival with this regimen was 1 year, and overall survival (OS) of 19 months in patients who experienced an objective response or stable disease [72].

Two separate Phase II studies evaluated the activity (objective response rate, PFS, OS) and toxicity of combining bleomycin, vincristine,

Table 2. Current adjuvant immunotherapy trials.

Clinical trials No.	Treatment	Phase	Eligibility	End point
NCT01100528 [†]	DTIC + IFN- α	II	Monosomy 3	Disease-free survival
NCT01585194 [†]	Ipilimumab	I/II	Class 2 gene expression or monosomy 3 + apical thickness ≥ 8 mm	MTD and overall response rate
NCT00929019 [†]	mRNA (gp100 and tyrosinase) transfected DC vaccine	III	Monosomy 3 and HLA-A2	Immunological response
NCT01983748 [‡]	DC plus autologous tumor RNA	I/II	Monosomy 3	Disease-free survival

[†]Completed study, results not yet reported.

[‡]Open to enrollment.

DC: Dendritic cell; DTIC: Dacarbazine; MTD: Maximum tolerated dose.

oral lomustine, dacarbazine, and either human leukocyte or recombinant interferon. These regimens, termed BOLD or BOLD-IFN, were studied in patients with metastatic UM who had either demonstrated progression of disease [73] or as first-line therapy [74]. In both studies, bleomycin 15 mg was given iv. on days 2 and 5, vincristine 1 mg/m² (2 mg maximum) iv. on days 1 and 4, lomustine 80 mg orally on day 1 and dacarbazine 200 mg/m² iv. on days 1–5. The BOLD chemotherapy was repeated every 4 weeks, pending recovery of hematologic and nonhematologic toxicities. Dosing of human leukocyte interferon and recombinant IFN- α -2b was similar at 3×10^6 IU subcutaneously once daily starting on day 8 of the first cycle and continuing for 6 weeks, followed by 6×10^6 IU three-times weekly. In both studies, patients who had received at least two cycles were assessable for response, using the WHO criteria [73,74].

The study utilizing human leukocyte interferon enrolled 22 patients, of which 20 were eligible for response assessment. Although no CR occurred, three patients (15%; 95% CI: 0–38) had a PR and 11 patients (55%; 95% CI: 32–77) had stable disease for a median of 7 months (range: 3.7–22 months). No table for this regimen, though, was the toxicity – 40% developed grade 3–4 hematologic toxicity, 35% with grade 2–3 constipation, and two treatment-related deaths occurred (septic infection with grade 4 leukopenia; myocardial infarction). Median PFS from the start of the treatment was 4.4 months (95% CI: 2–10) and OS was 12.3 months (95% CI: 8–22) [73].

The EORTC study utilizing recombinant IFN- α -2b enrolled 24 patients, of which 22 were evaluated for response. There were no objective responses, and only two patients (8.3%) had developed stable disease by the end of the protocol period. Although no treatment-related deaths occurred, all but one patient succumbed to progressive disease. The median PFS from the start of treatment was 1.9 months (95% CI: 1.8–3.4), and OS was 10.6 months (95% CI: 6.9–16.4) [74].

Due to the poor clinical activity of chemotherapeutic immunotherapy in UM, it is rarely utilized, clinically.

• Continuous IL-2

The efficacy and benefit of IL-2 has been better described in the cutaneous melanoma population, with varying doses and methods of

administration [75,76]. One Phase II trial enrolled 27 patients with metastatic melanoma, of which seven were primary UM, all with metastatic disease in the liver. IL-2 was given as a continuous iv. infusion at 18–20 million units/m²/day for 5 days, and repeated at the same doses after a 9-day rest period. Following this induction period, patients received maintenance therapy consisting of the 5-day continuous infusion IL-2 repeated every 3 weeks until progression of intolerance. Although six objective responses were seen among the patients, none occurred in the UM subset. All seven patients with liver metastases from UM progressed and died 3–5 months after starting continuous infusion IL-2 [77].

• Ipilimumab

Ipilimumab was US FDA-approved in 2011 for unresectable or metastatic melanoma, and became the first therapy proven to improve OS for these patients [78]. Early trials of ipilimumab for advanced melanoma excluded patients with UM, so activity in this particular patient population had been relatively unknown.

Multiple European groups have since evaluated the efficacy of ipilimumab provided through the expanded access program (EAP), as subgroup analyses. Enrolled patients had failed at least one prior therapy, and received ipilimumab 3 mg/kg iv. every 3 weeks for a maximum of four doses, and had responses assessed using RECIST version 1.1 and/or immune-related response criteria (irRC) [79]. Maio and colleagues evaluated 82 UM patients, of which four had an immune-related partial response (irPR) and 24 patients had immune-related stable disease (irSD), providing an immune-related disease control rate of 34%. Median PFS was 3.6 months (95% CI: 2.8–4.4) and OS was 6 months (95% CI: 4.3–7.7) [80]. Similar responses were seen with a UK study in five metastatic UM patients (as part of EAP), of which two patients had stable disease [81]. The Dutch immunotherapy working group (WIN-O), evaluated 22 patients with metastatic UM receiving this regimen of ipilimumab in their EAP. Of these 22 patients, there were no occurrences of CR, but one PR identified with RECIST and irRC, and one patient with stable disease per irRC. Median PFS was determined to be 2.9 months with an OS of 5.2 months [82]. The ipilimumab-ocular melanoma expanded access program (I-OMEAP) study group performed a subanalysis of metastatic UM patients who had received ipilimumab at a higher dose of

10 mg/kg iv. every 3 weeks for four doses (induction period). Patients were assessed with modified WHO (mWHO) criteria every 12 weeks beginning at week 12, and those determined to have clinical benefit at week 24 could receive maintenance doses of ipilimumab 10 mg/kg every 12 weeks. Of the 13 patients evaluated in this study, no objective tumor responses were identified. Nine patients completed the induction phase, of which two had stable disease. Interestingly, three patients with progressive disease (mWHO criteria) after the induction period continued on in the maintenance phase, and one patient had disease stabilization at week 24 which had remained at the time of analysis – 172 weeks after the first ipilimumab dose. Median overall survival for these 13 patients was 36 weeks (range: 2–172+ weeks) [83].

A multicenter, retrospective study assessed responses of ipilimumab at either 3 mg/kg or 10 mg/kg, in patients with metastatic UM who had received drug as part of a clinical protocol or via commercial supply at their respective institutions [84]. Of the 39 patients identified, 34 received ipilimumab at 3 mg/kg and the remaining five patients received 10 mg/kg doses. A total of 35 patients were included for response, but due to the mixed population of on- and off-protocol patients, tumor assessments were completed at slightly variable times. Twelve patients had scans completed at a median of 6.2 weeks, but the remaining patients were restaged at a median of 12 weeks. Responses were determined using mWHO and irRC criteria. At the week 12 assessment, there was one CR and 15 patients with stable disease using mWHO criteria, and one irCR and 17 patients with immune-related stable disease (irSD). One patient with irSD went on to develop irPR at approximately week 100. With a median follow-up of 12.6 months, the median OS was 9.6 months (95% CI: 6.3–13.4 months). A univariate analysis determined the ipilimumab dose of 3 mg/kg versus 10 mg/kg was not associated significantly with survival. Investigators did, however, identify a statistically significant difference in OS in comparison of patients with normal or low absolute lymphocyte count (ALC) at week 7. Of the 31 patients with ALC measurements at week 7, those with ALC ≥ 1000 cells/ μ l ($n = 22$) had a median OS of 13.4 months (95% CI: 9.6– ∞), while those with ALC < 1000 cells/ μ l ($n = 9$; $p = 0.004$) had a median OS of 4.8 months (95% CI: 3.6–7 months).

The Dermatologic Cooperative Oncology Group (DeCOG) also conducted an open-label, multicenter, Phase II trial to evaluate the efficacy and safety of ipilimumab 3 mg/kg iv. every 3 weeks for four doses in patients with metastatic UM. Tumor assessments were completed every 12 weeks starting at week 12, and responses were determined with RECIST version 1.1 criteria. A total of 53 patients were enrolled and received at least one dose of ipilimumab; eight patients (15%) were treatment-naïve and 45 patients (85%) had received at least one prior systemic therapy. A total of 34 of the 53 patients were eligible for response assessment, while 11 patients died prior to first restaging assessment. There were no CR or PR observed, and the disease control rate was determined to be 47% ($n = 16$) at week 12 and 21% ($n = 7$) at week 24. Median PFS was 2.8 months (95% CI: 2.5–2.9) and OS was 6.8 months (95% CI: 3.7–8.1). The primary end point of OS rate at 12 months was 22% (95% CI: 12–35). Investigators also determined that treatment-naïve patients did not have an improved 1- or 2-year survival as compared with patients who had been previously treated [85].

The Spanish Melanoma Group (GEM) conducted an open-label, Phase II study in metastatic UM patients, using front-line ipilimumab 10 mg/kg iv. every 3 weeks for four doses (induction period) followed by maintenance doses every 12 weeks until progression of disease or unacceptable toxicity. An interim analysis of 31 patients yielded 13 of which were evaluable for response; 1 PR (7.7%) was observed and six patients (46.2%) with stable disease, at a median follow-up of 5.5 months (95% CI: 3.4–11.1) [86].

In contrast to cutaneous melanoma, the retrospective and early-phase clinical studies of ipilimumab demonstrated disappointing clinical outcomes in UM, which may be explained by different tumor biology such as different metastatic tumor microenvironment (mainly the liver). In addition, total mutation burden can contribute to the difference. Recent data have demonstrated cutaneous melanomas exhibited the highest prevalence of somatic mutations [87], and higher somatic mutational burden of cancer was associated with clinical benefit from ipilimumab [88] or pembrolizumab [89]. Since a single agent ipilimumab may not induce disease control of advanced UM, several combinatorial approaches including a Phase II study of ipilimumab plus nivolumab (NCT01585194) are underway.

• Anti-PD-1

The use of antibodies targeting PD-1 has remarkably changed the landscape of managing advanced melanoma patients. As excitement continues with using these agents for advanced cutaneous melanomas, exploring efficacy in UM is a valid question. The Mayo Clinic evaluated seven metastatic UM patients who received pembrolizumab as part of an EAP, after progression of disease with previous ipilimumab therapy. Patients received the FDA-approved dose of 2 mg/kg iv. every 3 weeks until progression of disease or unacceptable toxicity, for up to 2 years, and were assessed with immune-related response criteria. Of the seven patients, there was one CR, one PR, and one patient with stable disease – this yielded an overall response rate (CR + PR) of 29% and disease control rate (overall response + stable disease) of 43%. Median PFS was reported at 12.2 weeks (range: 3.14–41) [90]. Currently, a Phase II study of pembrolizumab in advanced uveal melanoma is ongoing (NCT02359851).

• TIL therapy

Adoptive transfer of TIL was established as a safe and feasible therapy for metastatic melanoma since the early millennium [91]. Although initial studies failed to demonstrate an antitumor effect, augmentation of the conditioning regimen and optimization of TIL culture has led to several clinical studies demonstrating response rates upwards of 50% [92–95]. Those early studies failed to include patients with metastatic UM. Currently, however, the National Cancer Institute has a dedicated clinical trial using adoptive transfer of TILs (NCT0181404) for UM. MD Anderson, Moffitt Cancer Center, and other TIL centers may also be considering this population.

Conclusion

Despite the remarkable success of checkpoint blockade immunotherapy in cutaneous metastatic melanomas, this immunotherapeutic approach has very limited clinical activity in metastatic UM, which may be explained by multiple factors including the tumor immune

microenvironment (nearly always the liver), fewer mutation loadings, different mutational spectrum and different immunological aspects of tumors. Understanding the complex immune privilege of UM with further studies will allow us to find an effective therapeutic approach to overcome this potential resistance mechanism, and translate weak immune surveillance into robust antitumor immunity to mediate tumor rejection. The combination of checkpoint inhibitors and other immunotherapeutic agents, chemotherapy or molecularly targeted agents to reverse the immune suppressive environment of UM by increasing the number of effector T cells, enhancing function of exiting effector T cells, and stimulating innate immune systems may improve clinical outcomes in this resilient tumor.

Future perspective

Given the limited clinical activity of single agent immunotherapeutic approach, the combination of immunotherapeutic agents with different type of immunotherapy, chemotherapy or molecularly targeted agents will be studied to find effective approaches to control of advanced UM. Various biomarkers will be investigated to predict clinical responses and/or high grade adverse events to immunotherapeutic agents. Meanwhile, molecular biology and cancer immunology continue improvement of understanding the complex biological and immunological aspects of UM and the interaction between UM and the unique environment of the eye and the liver to guide development of novel immunotherapeutic approaches for the prevention and treatment of metastatic UM.

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