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Treatment of metastatic uveal melanoma

Mateusz M. Polaczek, Hanna Koseła-Paterczyk

Department of Soft Tissue/Bone Sarcoma and Melanoma; Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland

Uveal melanoma is a rare malignancy with a poor prognosis. The risk of metastatic disease (mainly to the liver) exceeds 50% and is often observed many years after the primary treatment. The methods of local surgical treatment of metastatic lesions in the liver provide some chance for long-term survival but are possible in a small percentage of patients. The therapies currently used as a standard for cutaneous melanoma are not as effective in ocular melanoma. The first drug that prolongs the survival of patients is tebentafusp, but its applicability depends on the presence of HLA-A*02:01 expression.

Key words: uveal melanoma, local treatment, immunotherapy

Introduction

Uveal melanoma (UM) is the most common primary neoplasm of the eye in adult patients [1–2]. Nevertheless, its occurrence is rare, and there are an estimated 2–11 cases per 1 million per year, with geographical differences [1–5]. UM differs from cutaneous and mucosal (including conjunctiva) melanoma; thus, the diagnostic and therapeutic approach is different [6].

Less than 3% of UM is present at the metastatic stage at primary diagnosis, and modern local treatment modalities offer high disease control rates [7–9]. Unfortunately, up to 70% of patients eventually develop metastases and will need systemic treatment [10, 11]. The recent advancement in the systemic treatment of metastatic cutaneous melanoma did not change the landscape of UM treatment; with median survival reaching 3 to 30 months in different studies and the 5-year survival rate under 20%, the necessity for improvement is evident [11–13].

This review discusses the monitoring and risk factors for metastatic disease development and current treatment approaches for metastatic uveal melanoma.

Follow-up for metastases and risk factors

After initial treatment, the patient requires follow-up, which should be considered for local recurrence and distant metastasis' monitoring. Local monitoring is typically performed during clinical visits of 3 to 6 months during the first two years and 6 to 12 months after that. This monitoring can be performed using ultrasound, magnetic resonance imaging (MRI), gonioscopy, and optical coherence tomography (OCT), depending on the resources and the primary treatment modality [14]. The rate of local recurrences is low, occurring in less than 10% [15–18]. It is also noteworthy to state that there is no evidence of increased risk for melanoma in the contralateral eye [5, 19], or for that matter, cutaneous melanoma, either [20].

Patients with uveal melanoma need many years of monitoring, and the risk of metastases steadily rises during a 20-year observation across stages I to III [11, 21]. In the COMS studies, the 2-, 5- and 10-year metastasis rates were 10%, 25%, and 34%, respectively, in the study population [22].

There is no commonly adopted observation schedule after local treatment for the disease's spread. The evidence for survival benefit in early detected (asymptomatic) metastases

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is not strong [23]. The patient's consent to undergo repetitive radiation-related tests should be obtained. The most important prognostic factor for metastases development is tumor size (based on AJCC TNM) [21]. Also, genetic information from the primary tumor can be informative: some known chromosomal abnormalities and several gene mutations are risk-related, separately or together [8]. A gene expression profile was proposed by Onken et al. [24]. The detailed description of clinical and genetic prognostic factors is summarized in table I [25–29]. Surveillance for high-risk patients should be made every 3 to 6 months during the first five years, then every 6 to 12 months until ten years, and yearly after that, although no evidence from prospective studies supports this [14]. Prospective studies have typically adopted a complete physical examination, chest X-ray, abdominal (liver) ultrasound, and liver function tests (LFTs) every six months [18, 22, 30, 31]. Other modalities commonly used in cancer patient monitoring have also been proven beneficial, although computed tomography (CT) and positron emission tomography/computed tomography (PET-CT) bear the risk of repetitive exposure to radiation; on the other hand, liver MRI has high sensitivity in detecting liver metastases in the early stage [32, 33]. LFTs are being debated [33–35], in the COMS study, the alkaline phosphatase (ALP), considered the most useful, has a sensitivity of only 14.7% at the time of final testing before the metastatic disease was revealed with imaging studies [22].

Liver metastases are the primary and most expected place of uveal melanoma spread in up to 90% of cases [36]. The rates of other sites are much lower; for the lungs, bones, skin, and lymph nodes, it varies – around 20%, 16%, 11%, and 10%, respectively. The rate of brain metastases is considered very low, under 5%; thus, no routine brain monitoring is indicated during the follow-up [22, 37, 38].

Metastatic disease characteristics and workup

At the time of diagnosis of metastatic disease, a biopsy is encouraged. This material will confirm the diagnosis and serve for molecular findings, which may navigate the treatment choices and is often mandatory for enrollment in clinical trials. Chest to pelvis CT or full-body PET-CT may assess the spread of the disease if only liver involvement is suspected. Blood work is also routinely done. Early detection of the human leukocyte antigen (HLA) A*02:01 allele can benefit future decision-making.

Different negative prognostic factors for survival in stage IV were identified: older age, male sex, and poor performance status [13, 30, 31]. Also, elevated ALP and lactate dehydrogenase (LDH) are believed to be negative prognostic factors [13, 30, 39, 40]. The symptomatic patients also have a poorer prognosis, either those with a shorter time to progression and more disease burden [13, 30, 31]. Careful consideration of these prognostic factors helps to select who will benefit from treatment and who should only be offered supportive care.

Many treatment approaches for UM can be divided into local, i.e., liver-oriented and systemic methods. `Therapy selection should be based on the involved sites and the number of metastases: a small disease burden may result in complete response and more prolonged survival [40, 41]. Local modalities have led to longer median overall survival in clinical studies. That said, until now, the only UM-oriented treatment with FDA and EMA approvals is for a bispecific antibody – tebentafusp, which has shown meaningful survival benefits in a recently published clinical trial [42–44].

Local treatment

Local treatment should be offered to patients with isolated liver involvement of UM. There are different methods used in this setting. The clear numerical benefit of prolonged overall survival observed in many studies of isolated hepatic metastases treatment may be partly related to patient selection bias [45–47]. Nevertheless, meaningful disease-free survival is observed in some patients when a complete response is obtained. Thus, the median overall survival (OS) in many trials exceeded 20 months and reached 35 months in one [45–47].

Table I. Known genetic alteration in uveal melanoma cells and their postulated prognostic role for disease spread and survival [24–29]

Genetic alteration	Clinical information
Onken et al. class 2 gene expression profile: the assay includes 12 discriminating genes and is prognostic regardless of chromosome 3 status	5 to 20 times higher risk of metastatic disease for class 2
chromosome 3 disomy, chromosome 6p gain	better prognosis
chromosome 3 monosomy, chromosome 8q gain	increased risk of metastatic disease, risk rises when both are present
loss of chromosome 8p, loss of 1p, loss of 16q and loss of 6q	increased risk of metastases
gain of chromosome 6q (with the presence of chromosome 3 monosomy and chromosome 8q gain)	decreased risk of metastases in the presence of unfavorable genetic alterations
EIF1AX mutations	low risk of metastases
SF3B1 mutations	medium risk of metastases
BAP1 mutations or loss of BAP expression	high risk of metastases
preferentially expressed antigen in melanoma (PRAME) expression	increased risk of metastases

Surgical resection of metastases should be offered to patients with 1–2 lesions which are possible for R0 resection. In other cases, surgical techniques and local procedures should be considered [47].

Perfusion techniques are used to administer a high dose of a cytotoxic agent through the hepatic artery; during open surgery – isolated hepatic perfusion (IHP) or less invasive procedures – percutaneous hepatic perfusion (PHP) and hepatic arterial infusion (HAI) [41, 47]. These methods result in moderate response rates (40–60%), with low rates of morbidity (<10%), and can be repeated if indicated [41, 47].

The embolization approach combines the use of cytotoxic agents (hepatic chemoembolization), immunotherapy (immunoembolization), or radiation techniques (transarterial radiation with yttrium-90) with the induction of ischemia [41, 48]. Multiple retrospective and prospective studies confirmed a high disease control rate after radioembolization (under 50%), even when used after previous local treatment failure [49–51].

The ablative procedures are used in complex tumors; they have low rates of complications, the most common being radiofrequency ablation (RFA) and microwave ablation (MWA). The ablation procedures offer modest efficacy, with survival time exceeding 20 months in most retrospective reports [52, 53].

When a complete response is achieved, patients can be offered adjuvant treatment in clinical trials. In all other cases, the observation algorithm remains similar to the high-risk patients after the primary treatment (discussed above).

Systemic treatment

Many treatment approaches were tested for metastatic UM, including cytotoxic agents, targeted therapies, and immunotherapy. Small phase II and some phase III studies often delivered conflicting results. Thus, patients with advanced UM should be offered participation in clinical trials whenever possible.

Different cytotoxic agents can be used in monotherapy and combinations, most commonly dacarbazine (DTIC), paclitaxel, temozolomide, fotemustine, bendamustine, treosulfan, vincristine, arsenic trioxide, and lenalidomide [14]. Combination therapies often contain the platinum compound. Objective responses for monotherapy are rarely observed; the highest objective response rate (ORR) of 20% was demonstrated in a minor study of cisplatin/dacarbazine/vinblastine combination, with a median progression-free survival (PFS) of 5.5 months and OS of 13.0 months [54]. This need to be interpreted with caution because no other trial of cytotoxic agents, even in combinations, has failed to reach over 6% ORR [55–58]. Based on meta-analyses, chemotherapy results in ORR of around 4% with poor PFS of 2.6 months and median OS of 9 to 11 months [13, 59, 60]. In an interesting EORTC 10821 study, patients with isolated liver metastases were randomized to obtain local HAI or systemic treatment with fotemustine. The median OS was not different between the treatment arms (14.6 months *vs.* 13.8 months), and it seemed that the main factor for survival benefit was the disease burden and not the treatment itself [61].

Molecular alterations in UM cells are distinct from cutaneous melanoma, most notably KIT overexpression and GNAQ and GNA11 mutations resulting in MAP kinase activation [6, 62–64]. Many single-arm trials were conducted using targeted therapies, including imatinib (for KIT) [65–67], trametinib [68], and selumetinib (MEK inhibitors, the latter is not registered for use by FDA nor EMA) [69, 70], and many others. No meaningful benefit was demonstrated, and it is widely accepted that targeted therapies did not significantly improve survival over chemotherapy. The combination of chemotherapy and targeted agents also failed to achieve any PFS or OS prolongation [70–72].

Immunotherapy remains the best out of all poor options for metastatic UM. Although unlike cutaneous melanoma, no significant benefit was seen with single-agent anti-CTLA-4 antibodies ipilimumab and tremelimumab [73, 74], nor with single-agent anti-PD-1 antibodies nivolumab and pembrolizumab (ORR under 10%) [75–77]; some more hope was seen with the nivolumab/ipilimumab combination. Lately, breakthrough results of the phase III study of tebentafusp have been published [44].

As for the nivolumab/ipilimumab combination, one phase II study reported a median OS of 19.1 and median PFS of 5.5 months [78], which is numerically high compared to all past studies. Also, ORR was relatively high – 18%. These results were not repeated in the second nivolumab/ipilimumab trial, and further investigation is needed [79].

Tebentafusp, previously known as IMCgp100, was tested in a phase III randomized trial. Patients with HLA-A*02:01 expressing T-cells (about 45% of the screened population) were randomized 2:1 to receive tebentafusp or investigator choice treatment (monotherapy with pembrolizumab, ipilimumab, or DTIC). The study demonstrated a significant survival benefit at one year: 73% *vs.* 59%, which translated into a hazard ratio (HR) for death of 0.51 (95% CI: 0.37–0.71, $p < 0.001$). Median OS was prolonged from 16.0 months in the control arm to 21.7 months in the tebentafusp arm, despite a cross-over being allowed. It is also noteworthy that 43% of tebentafusp patients continued the treatment post-progression. A moderate benefit was also seen in median PFS prolongation from 2.9 to 3.3. Nevertheless, the ORR was relatively low, only 9% in the investigated arm. The toxicity profile was manageable, with no treatment-related deaths and only 2% of events that led to treatment discontinuation in the tebentafusp arm. Cytokine release syndrome, related to tebentafusp infusion, is prevalent during the first few cycles (occurs in more than 30% of patients); the injection needs to be monitored in the hospital [42–44].

Conclusions

Local therapies should be considered the best option when suitable for metastatic UM, despite the efficacy not being

confirmed in randomized trials. The recent approval of tebentafusp has impacted the treatment landscape of UM, but the requirement of HLA-A*02 positivity will limit its use. This orphan disease still has an inferior prognosis at the metastatic stage, and the need for new compounds is high.

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Mateusz M. Polaczek
Maria Sklodowska-Curie National Research Institute of Oncology
Department of Soft Tissue/Bone Sarcoma and Melanoma
ul. Roentgena 5
02-781 Warszawa, Poland
e-mail: mateusz.polaczek@pib-nio.pl

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