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Review

Therapy Resistance and Failure in Uveal Melanoma

Senmao Li[a] Yongwei Guo[b] Philomena A. Wawer Matos[a,c] Alexander C. Rokohl[a,c] Ludwig M. Heindl[a,c]

[a]Department of Ophthalmology, University of Cologne, Faculty of Medicine and University Hospital Cologne, Cologne, Germany, [b]Eye Center, School of Medicine, Second Affiliated Hospital, Zhejiang University, Hangzhou, China, [c]Center for Integrated Oncology (CIO) Aachen-Bonn-Cologne-Duesseldorf, Cologne, Germany

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Abstract
Uveal Melanoma (UM), a common malignant intraocular tumor, is currently lacking a standard therapy. Traditional surgical approaches can result in patients losing organs or having difficult surgical procedures resulting in poor postoperative outcomes. Either way, there is no improvement in patients' quality of life after surgery compared to radiotherapy. As a first-line treatment with radiotherapy, this therapy is limited by the size and location of the tumor. The risk of postoperative vision loss and second surgery for enucleation remains. UM is a special type of melanoma that is resistant to chemotherapy, and although the treatment is not effective, research has been investigated on this topic, suggesting new ideas for the treatment of UM - immunotherapy and targeted therapy. The current nivolumab plus ipilimumab treatment regimen has yielded relatively successful results, with some very encouraging case reports, but not as good as their efficacy in skin cancer. Despite the current unsatisfactory results of these new therapies, it is still the most attractive answer for UM that is highly metastatic and has a very poor prognosis. This review supports clinical decision-making and new treatment development by compiling the strengths and weaknesses of common treatments currently available in the clinic.

Introduction

Uveal Melanoma (UM), the most common malignant intraocular tumor in adult Caucasians, originates from melanocytes of the uvea, including the iris, ciliary body, and retinal choroid [1]. The incidence of UM has remained relatively stable since the 1970s at approximately 5.1 per million individuals in the United States [2]. Some studies reported the increased incidence in northern European white populations [3, 4]. Preserving the eye and

Prof. Ludwig M. Heindl
Department of Ophthalmology, University of Cologne,
Faculty of Medicine and University Hospital Cologne,
Kerpener Strasse 62, 50937, Cologne (Germany)
Tel. +49 221 478 42909, Fax +49 221 478 81350, E-Mail ludwig.heindl@uk-koeln.de

good vision is the priority of eye treatment, consisting of various forms and combinations of phototherapy and radiotherapy [5]. Once it is life-threatening in advanced cases, local resection and enucleation are also essential [5]. Effective in treating primary lesions in more than 95% of cases, unfortunately, distant recurrence was spotted in up to half of the cases [6]. The liver is the most common site of metastasis, and lung, bone, and skin/subcutaneous tissue are also reported [7, 8]. The poor prognosis is highly related to systemic metastases. Approximately 20% - 30% of patients with a primary uveal melanoma die of systemic metastases within five years of diagnosis, nearly half dead within 15 years [2, 6].

To improve prognosis, many novel approaches to the management of UM have been developed in the past few decades. During the exploration, some unexplainable phenomena emerged that UM tends to be characterized by chemoresistance. Since most treatments for metastatic UM have been extrapolated from experience with cutaneous melanoma, such a finding is certainly a major blow to researchers. Until now, there are no US Food and Drug Administration (FDA)-approved systemic therapies for uveal melanoma in the adjuvant or metastatic settings, and no therapy has been shown to improve overall survival. This review is to summarize different treatment approaches and discuss treatment resistance and failure in UM treatment.

Surgery: Attempt of traditional treatment

Enucleation

Enucleation, as a last resort approach, especially a standard treatment in the past, is replacing radiation therapy (i.e., brachytherapy with radioactive plaques or external-beam, charged-particle radiation therapy) to spare the affected eye [9, 10]. The negative aspects of enucleation include worsening visual functions (such as peripheral vision, having difficulty night driving, or judging distances), a greater decrease in role functioning, and larger physical and functional well-being reductions. Based on clinical results, the survival is not significantly improved with enucleation between cobalt plaque brachytherapy [11-15], a mix of brachytherapy plaque types [16], or proton-beam radiotherapy [17]. Compared with proton-beam radiation or stereotactic radiosurgery (SRS), enucleation has similar overall survival, metastasis-free survival, and melanoma-related mortality [18-21]. Overall, it seems that there are no more advantages to enucleation than relatively low technical difficulties.

Surprisingly, many studies showed that enucleation might have similar quality of life as those treated with RT [22-26]. Furthermore, it is still recommended for patients unsuitable for brachytherapy treatment, such as tumors with optic nerve involvement or massive tumors that clinical plaques could not effectively treat. When local recurrence or complications occur after primary treatment with preserved eyes, enucleation is recommended as well.

Local resection

Unlike the enucleation, local resections, including transretinal (endoresection) and transscleral (exoresection) approaches, are aimed at conserving the eye and useful vision [27-29]. However, in the NCCN Guidelines, local resection is not recommended for uveal melanoma as a primary treatment option for choroidal or ciliary body melanoma [30]. Mostly because the local resection is technically challenging, and a case report showed even transretinal tumor biopsy bears the potential risk for tumor cell seeding [31]. Immediate postoperative complications are common, such as hemorrhage, retinal detachment, ocular hypertension, and proliferative vitreoretinopathy, which may require repeat surgery [27-29]. This treatment relies more on the individual surgeon's skill and does not benefit the entire patient group.

Radiotherapy: challenging but effective

Radiotherapy is currently the main treatment for UM [2]. As mentioned previously, although the results are similar to enucleation, radiotherapy is very popular due to the trend towards eye preservation. The prospective randomized trials for collaborative ocular melanoma (COMS) are valuable, with the main consideration being the size and location of the tumor. The result of COMS shows that patients with choroidal melanomas like 2.5–10.0 mm in apical height (2.5–8.0 mm if peripapillary) and ≤16 mm in maximum basal diameter, no extrascleral extension ≥2mm thick, will not significantly benefit more from enucleation comparing with RT [32, 33].

For ease of understanding, tumor size is categorized in this paper as referenced to NCCN [30]. The small tumor is thickness under 2.5mm and largest diameter 5-18mm. The medium tumors are thickness 2.5–10 mm, diameter ≤18 mm. The large tumors are height ≥2mm, and diameter >18mm; or height >10mm, and any diameter; or height >8mm, any diameter, if proximal tumor border <2 mm to the optic disc.

According to different studies, the local failure rate of different types of brachytherapy plaques (Iodine-125, ruthenium-106, palladium-103, cesium-131) is less than 24% for small size tumors [34-39]. However, the possibility of recurrence after 12 years has been reported [37]. For tumors of medium size, there is essentially no difference in all-cause mortality or death with confirmed melanoma metastasis 5 to 15 years after surgery [33]. Risk factors for treatment failure were older age, greater tumor thickness, and tumor proximity to the foveal avascular zone [30].

In addition to postoperative local recurrence, intraoperative complications can occur. Pain requiring medication; other hemorrhages; cardiovascular or pulmonary problems; urinary problems; and local surgical problems are common intraoperative/immediate postoperative complications observed in both brachytherapy and enucleation [32]. However, intraocular hemorrhage, scleral perforation, and vortex vein rupture are only occurred in brachytherapy [32]. Besides that, the most common and important long-term complications were loss of visual acuity and growth of tumor or other indications that lead to enucleation [32]. Posterior vision loss is the most serious complication of RT, as preservation of vision is the main advantage of RT compared to enucleation. After three years of follow-up, approximately half of the patients (49%) treated with brachytherapy lost over six lines of visual acuity [40], and vision loss is associated with greater baseline tumor apical height, shorter distance between the tumor and the foveal avascular zone, presence of tumor-associated retinal detachment, non-dome-shaped tumor, and patient history of diabetes [40]. Approximately 12% of patients need an enucleation in a 5-year following up, and most of them suffer from brachytherapy failure and eye pain [40, 41]. Recent prospective studies showed that applicator size, basal tumor diameter, juxtapapillary location, dose (close to foveola or retinal), increased tumor height, radiation maculopathy, and radiation optic neuropathy are associated with loss of visual acuity after brachytherapy [42-44].

Chemotherapy: unexpected resistance

Most treatments for metastatic UM refer to the experience with cutaneous melanoma [45]. The most commonly used drugs in conventional chemotherapy have been dacarbazine, fotemustine, and temozolomide. On the other hand, studies have also been conducted with more modern agents, such as docosahexaenoic acid and paclitaxel, and liposomal vincristine [46].

However, the biology, clinical presentation, pathological features, prognosis and metastasis of UM and CM are distinctly different. Many agents, including dacarbazine, temozolomide, cisplatin, treosulfan, fotemustine, and various combinations, have demonstrated fewer effects on survival, with response rates ranging between 0 and 15% [47-49].

Recent studies on temozolomide and dacarbazine showed that the medians of overall survival are under 13 months and progression-free interval of up a maximum of 5.5 months [50-54]. Although these results are not as good as expected, the combination of treosulfan and gemcitabine reached medians of 14 months and annual survival rates of 80% [55]. There are still some relatively successful individual cases reported with Chemotherapy. A study by Leyvraz et al. reported one patient lived five years with fotemustine [56]; in the trial by Terheyden et al., a patient survived 57 months with gemcitabine and treosulfan [57]; and in the study by Schinzari et al., a patient survived 72 months with a combination of cisplatin and dacarbazine [58].

Besides the unsatisfied results, chemotherapy has a negative impact on patients' quality of life, with approximately half of the patients experiencing toxic reactions in the form of nausea and vomiting [59]. Compared to RT, the benefits for chemotherapy patients are not high.

To this day, the principle of chemotherapy resistance in UM remains unclear. Different hypotheses suggest that the immune privileges of eyes that indulge the growth and development of complex tissues. The resistance might attribute to different mechanisms of immune response inhibition. To avoid chemotherapy resistance, many researchers aimed at immunotherapy.

Immunotherapy & Targeted therapy: promising future?

Immunotherapy has been shown to have a considerable survival benefit in treating metastatic cutaneous melanoma since 2011. However, the response rates and survival outcomes of both immune checkpoint inhibition and molecularly targeted therapy are very different in UM [60].

Ipilimumab, a monoclonal antibody to cytotoxic T-lymphocyte antigen 4 (CTLA-4), blocks the effects of this regulator and increases T-cell responses against cancer cells. Although ipilimumab increases immune system performance and benefits in metastatic skin melanoma survival [61], the survival of UM is not increased with average values of nearly ten months [50, 62]. The overall survival and progression-free interval of anti-PD1 (anti-receptor of programmed death) therapy, such as pembrolizumab or nivolumab, are similar to ipilimumab [50, 63].

Combining several immunotherapies gets better outcomes. Kirchberg et al. [64], (Ipilimumab + Pembrolizumab), and Pelster et al. [65], (Nivolumab + Ipilimumab), reported median overall survival of 18.4 and 19.1 months, respectively. Najjar et al. study showed that dual checkpoint inhibition yielded higher response rates than previous reports of single-agent immunotherapy in patients with metastatic UM, but the efficacy is lower than in metastatic cutaneous melanoma [66]. Pelster et al. suggested the combination regimen of nivolumab plus ipilimumab demonstrates activity in metastatic uveal melanoma, with deep and sustained confirmed responses [67]. The most encouraging results were reported by Klemen et al., in which 20% of patients reach five years of survival [68]. This result might come out with receiving anti-CTLA-4 and anti-PD-1, either sequentially or in combination, or the selection of the patients, or to a reduced number of the samples.

Many potential new therapies are also being investigated. Recent research brings out a treatment with tebentafusp resulted in longer overall survival, which is a bispecific protein consisting of an affinity-enhanced T-cell receptor fused to an anti-CD3 effector that can redirect T cells to target glycoprotein 100–positive cells [69]. There is a study suggest that MHC II uveal melanoma vaccines activate purified CD4+ T cells and may serve as a novel immunotherapy for uveal melanoma patients [70].

Glembatumumab vedotin, a transmembrane protein which is highly expressed in multiple tumour types, is a fully human monoclonal antibody against glycoprotein nonmetastatic B (GPNMB). In a recent study, Glembatumumab vedotin benefited in metastatic UM treatment and was well-tolerated in the metastatic UM patient population [71].

Infusion of autologous TILs is a potential treatment [72]. In Chandran et al. study, the transfer of reactive TILs could induce tumour regression in patients with metastatic UM, and this suggested adoptive transfer of TILs with threshold production of INF-gamma might related to objective tumour regression [73].

Targeted therapy refers to drugs designed to interfere with a specific molecular pathway that is believed to play a critical role in tumor development or progression. UM has a distinctive genetic profile that makes it an attractive candidate for the treatment with molecular target therapy [74]. The targeted therapies explored mitogen-activated protein kinase (MAPK) inhibitors, such as sunitinib, sorafenib, imatinib, cabozantinib, and selumetinib [40] alone or in combination with chemotherapy, and the results of median overall survival are range from 3 to12 months [51, 75-78]. KIF15, belonging to the kinesin-12 family, plays a positive role in the tumorigenicity of melanoma and it may serve as a novel diagnostic and therapeutic target for melanoma, especially uveal melanoma [79].

Due to the metastability of UM, immunotherapy is the hot spot of UM research. However, there is no standard-of-care therapy, and participation in a clinical trial should be prioritized for metastatic UM patients. For patients who are not eligible for or decline clinical trials, combination immunotherapy with nivolumab plus ipilimumab benefits more than single-agent immunotherapy.

Liver directed therapies: hope of metastatic uveal melanoma

The hepatotropism of UM contributes to the development of liver-directed therapy methods.

Hepatic metastasectomy required experience, techniques, and patients should in good physical condition for general anaesthesia with less 10% liver uveal metastasis. Fortunately, hepatic metastasectomy is able to almost double the survival and appears at present the optimal way of improving the prognosis in metastatic uveal melanoma. According to Mariani et al. study, the median OS of 14 months extended to 27 months after microscopically complete resection [80]. Those who with poor surgical canditions and a small number of liver lesions, could try radiofrequency ablation. Although the survival time is not improved, OS in patients with less than 6 metastatic liver lesions reached 19.3 months [81, 82].

Thanks to the dual blood supply in the liver, other liver-directed therapies are able to reach the metastases via the hepatic artery directly. Intrahepatic therapeutic methods include bland embolization, intra-arterial administration of chemotherapies, intra-arterial hepatic chemoembolization, radioembolization, immune embolization and intra-arterial hepatic perfusion.

Intra-arterial hepatic perfusion can be done by IHP, or by percutaneous IHP (PHP). However, IHP is not a repeatable open surgical technique, while PHP is minimally invasive and repeatable. Liver-directed therapies allow high doses of medicines to be delivered locally while decreasing systemic toxicity, ensuring a comparable oncologic therapy impact with less morbidity and the ability to be repeated throughout the treatment duration [83-85]. Although there is a lack of prospective data on the efficacy of liver-targeted treatments, studies have shown some therapeutic value. Even after adjusting for prognostic variables, a meta-analysis showed that liver-focused therapy had a significantly higher 6-month PFS than chemotherapy, immunotherapy, and targeted therapy [86].

Conclusion

There are currently various methods of managing UM, and choosing the appropriate clinical treatment regimen for the situation is now a requirement for providing a good prognosis. There is no single perfect treatment for all clinical management of UM, and chemoresistance remains a problem to be explored, providing researchers with

new challenges and opportunities. When we can fully understand the mechanisms of chemoresistance in the future, we will be able to understand the essence of UM more deeply and thus develop effective treatments or have a deeper understanding of the human immune system. At the current level of medical technology, the need for personalized UM treatment has emerged. Although treatment failures and resistance exist, these clinical cases provide evidence for more precise treatment in the future. Both clinicians and researchers should remain curious to find out the reason behind each unusual case to seek more satisfactory treatment results.

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Conception and design: Senmao Li, Ludwig M. Heindl; (II) Administrative support: Ludwig M. Heindl; (III) Provision of study materials: Ludwig M. Heindl, Alexander C. Rokohl, Senmao Li; (IV) Collection and assembly of data: Alexander C. Rokohl, Senmao Li; (V) Data analysis and interpretation: Ludwig M. Heindl, Philomena A. Wawer Matos, Senmao Li; (VI) Manuscript writing: Senmao Li; (VII) Final approval of manuscript: All authors.

Disclosure Statement

The authors have no conflicts of interest to declare.

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