Immunoembolization for the Treatment of Uveal Melanoma Hepatic Metastases

Carin F. Gonsalves, MD, FSIR[1]

[1] Interventional Radiology, Thomas Jefferson University, Philadelphia, Pennsylvania

Semin Intervent Radiol 2024;41:20–26

Address for correspondence Carin F. Gonsalves, MD, FSIR, Interventional Radiology, Thomas Jefferson University, 132 South 10th Street, Main Building, Suite 766, Philadelphia, PA 19107 (e-mail: Carin.gonsalves@jefferson.edu).

Abstract

Uveal melanoma is the most common primary intraocular tumor in adults. Approximately 50% of patients develop metastatic disease despite successful treatment of the primary eye tumor. The liver is the most common site of metastatic disease occurring in more than 90% of patients. Clinical prognosis is dependent on the ability to control the growth of liver tumors. Locoregional therapies play an important role in stabilizing liver metastases, prolonging survival for patients with metastatic uveal melanoma. As overall survival is prolonged, the development of extrahepatic disease becomes more common. Immunoembolization, a form of liver-directed therapy, not only focuses on treating hepatic metastases by stimulating the local immune system to suppress the growth of liver tumors, but it potentially generates a systemic immune response delaying the growth of extrahepatic metastases as well. The following article discusses immunoembolization for the treatment of metastatic uveal melanoma including the rationale, mechanism of action, indications, contraindications, outcomes, and associated toxicities.

Keywords

- uveal melanoma
- immunoembolization
- granulocyte macrophage-colony-stimulating factor
- liver-directed therapy
- interventional radiology

Uveal melanoma is the most common primary intraocular tumor in adults with an annual incidence of 5.2 per million population.[1] Men have a higher age-adjusted incidence than women with 6.0 per million population compared with 4.5 per million population, respectively.[1] The median age at the time of diagnosis is 62 years, with a peak age range between 70 and 79 years. Ninety-eight percent of patients who develop uveal melanoma are Caucasian with rare cases occurring in other races and ethnicities.[1]

Risk factors for developing uveal melanoma include fair skin; inability to tan; light eye color; cutaneous, iris or choroidal nevi; oculodermal melanocytosis; and the presence of germline BRCA 1-associated protein mutations.[2] Sunlight exposure has not been unequivocally implicated as a risk factor for developing uveal melanoma.[2,3] However, arc welding is a known environmental risk factor for developing the disease.[2,3]

Uveal melanoma develops from melanocytes located in the uveal tract with 4, 6, and 90% arising from the iris, ciliary body, and choroid, respectively.[2] Uveal melanomas are often found incidentally on ophthalmologic examination. However, patients may also present with symptoms such as floaters, photopsia, metamorphopsia, blurred vision, and visual field defects.[2] The most common treatment for uveal melanoma is plaque radiotherapy achieving tumor control in greater than 92% of patients.[2] Enucleation is recommended for larger diameter and thicker tumors, extraocular extension, and for patients with pain or poor visual acuity at presentation.[3]

At the time of primary eye tumor diagnosis, detection of metastatic disease is uncommon occurring in less than 2% of patients.[4] However, metastatic disease via hematogenous spread occurs in up to 50% of patients despite successful treatment of the primary eye tumor. Patients at increased risk for metastatic spread include male gender, advanced age at presentation, ciliary body tumors, larger diameter and thicker tumors, extraocular tumor extension, intraocular hemorrhage, and the presence of subretinal fluid.[2] In addition, cytogenetic alterations, including monosomy 3 and 8q amplification, are associated with an increased metastatic risk and a poor prognosis.[5–7] Monosomy 3 is detected in

Issue Theme Liver Cancer (Part 2); Guest Editor, Donna L. D'Souza, MD

Thieme Medical Publishers, Inc., 333 Seventh Avenue, 18th Floor, New York, NY 10001, USA

DOI https://doi.org/10.1055/s-0043-1777712.
ISSN 0739-9529.

~65% of tumors and is associated with a 5-year survival of 37%.[5] Patients with tumors expressing at least one 8q amplification have a 5-year survival of 29%.[5] The presence of both cytogenetic alterations is associated with an extremely poor prognosis. Gene-expression profiling is an important prognostic indicator of metastatic risk proving to be even more accurate than the previously described clinical factors or cytogenetic alterations. A commercially available 15-gene expression profile developed by Castle Biosciences (Friendswood, TX) divides primary uveal melanomas into two classes. Class 1 indicates a low risk of metastatic disease, while Class 2 indicates a high risk of metastatic disease.[8,9] Class 1 tumors are further subdivided into Class 1a and 1b. The 5-year risk of metastatic disease is 2, 21, and 72% for patients with Class 1a, Class 1b, and Class 2 tumors, respectively.[6] The process has been recently refined and modified to employ a 12-gene expression profiling assay along with the analysis of PRAME mRNA expression. Class 1 PRAME-negative tumors, Class 1 PRAME-positive tumors, and Class 2 tumors have a reported metastatic risk of 0, 38, and 71%, respectively.[10]

For patients who develop metastatic disease, the liver is the predominant organ of involvement in more than 90% of patients and ~50% of patients will develop extrahepatic metastases within a median of 4.4 months (range, 1.1–17.1 months).[11] Unfortunately, less than 10% of patients with liver metastases are eligible for surgical resection or ablative therapies due to the presence of multiple tumors at the time of diagnosis (►**Fig. 1**). Clinical prognosis following the development of hepatic metastases is dependent on the ability to control the growth of liver tumors. Historically, prior to the advent of liver-directed therapies, survival for patients with hepatic metastases ranged between 2 and 9 months.[11,12] More recently, locoregional therapies, including immunoembolization, chemoembolization, radioembolization, and percutaneous hepatic perfusion, have been successful in controlling the growth of hepatic tumors, prolonging the survival of patients with uveal melanoma hepatic metastases.[13–20] This article discusses immunoembolization for the treatment of metastatic uveal melanoma including the rationale, mechanism of action, indications, contraindications, outcomes, and associated toxicities.

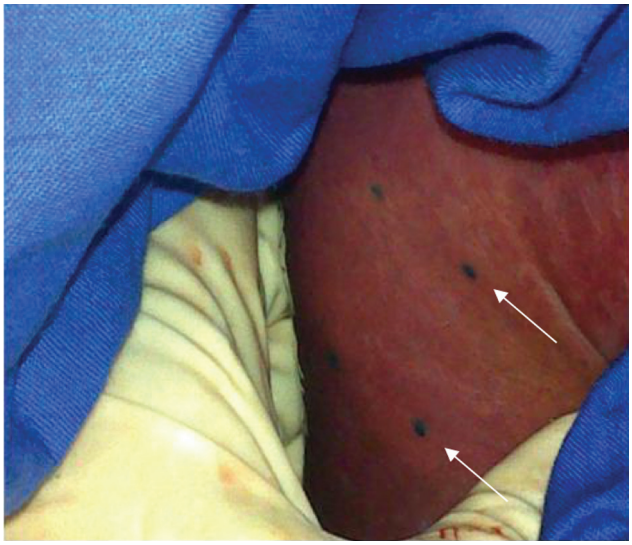

Fig. 1 Multiple melanoma metastases on the surface of the liver (arrows) in a patient undergoing surgical resection for a presumed solitary tumor.

Immunoembolization

Background and Rationale

Historically, there have been no effective systemic therapies for the treatment of metastatic uveal melanoma. Chemoembolization was the first liver-directed therapy used to successfully control the growth of liver tumors.[13–15] However, chemoembolization is limited by cumulative toxicities and is also incapable of preventing the progression of extrahepatic metastases necessitating the development of a modified approach to treat this disease.

Immunoembolization offers several advantages beyond the ischemic effect caused by embolization itself. The concomitant administration of a biological response modifier, also known as an immunomodulator, is intended to promote an inflammatory response within both the targeted tumors and the adjacent hepatic parenchyma, thereby attracting and stimulating antigen-presenting cells. In turn, this inflammatory response facilitates antigen uptake released by necrotic tumor cells, enhancing the local immune system's ability to recognize and destroy residual tumor cells within the liver. In addition, stimulation of the local immune system can potentiate a systemic immune response against tumor cells, thereby suppressing the growth of non-targeted tumors, specifically extrahepatic metastases. In other words, immunoembolization has the ability to potentially create an *in situ* tumor vaccine.

The concept of immunoembolization was first developed in Japan for the treatment of hepatocellular carcinoma using a penicillin-killed and lyophilized preparation of a low virulence strain of *Streptococcus pyogenes* known as OK432 (Chugai Pharmaceuticals, Tokyo, Japan). Several reports describe encouraging results following embolization with OK432, fibrinogen, and ethiodized oil, along with infusion of immature dendritic cells stimulated with OK432 followed by embolization.[21–24] Furthermore, in a series of six patients, resection of hepatic tumors following immunoembolization demonstrated massive tumor infiltration of mononuclear cells in conjunction with tumor necrosis.[21] Based on these findings, our group adopted the concept of immunoembolization and modified its technique as OK432 was not commercially available in the United States.

Granulocyte macrophage-colony-stimulating factor (GM-CSF) is a glycoprotein predominantly secreted by activated T-cells that stimulates macrophages, promotes maturation of dendritic cells, and increases the cytotoxicity of monocytes toward tumor cell lines. GM-CSF was selected as the cytokine of choice for immunoembolization based on a study by Dranoff et al that compared the vaccination properties of murine tumor cells transduced with ten retroviruses encoding different potential immunomodulators.[25] In this study, irradiated B16 melanoma cells alone generated no antitumor

immunity. However, new tumors were prevented and established tumors regressed in mice injected with irradiated B16 melanoma cells containing the transduced GM-CSF gene. The antitumor immunity was also found to be potent, specific, and long-lasting maintaining a presence several months after injection of B16 melanoma cells producing GM-CSF. This antitumor activity was attributed to the effect of GM-CSF on the maturation and/or function of dendritic cells. GM-CSF was also found to be the most potent stimulator of systemic anti-tumor immunity of the 10 molecules tested by Dranoff et al.

Based on the results of this study and the important role GM-CSF plays in the immune system, our group hypothesized that GM-CSF emulsified with ethiodized oil could be administered intra-arterially to treat uveal melanoma hepatic tumors and potentially induce systemic immunity against melanoma cells to prevent or slow the growth of extrahepatic metastases.

Literature Review

Immunoembolization using GM-CSF was first shown to be safe in a study utilizing a normal porcine model.[26] Subsequently, our institution conducted a dose-escalating Phase I (2000–2004) trial to investigate the safety of treating metastatic uveal melanoma patients with immunoembolization.[27] Thirty-four patients with less than 50% hepatic tumor burden were enrolled in the study. Patients underwent lobar treatments at 4-week intervals using 25 to 2,000 μg of GM-CSF emulsified in ethiodized oil followed by gelatin sponge embolization. Contrast-enhanced MRI and CT were performed after every two treatments to evaluate for tumor response and extrahepatic disease. The primary endpoints in this study were dose-limiting toxicity and maximum tolerated dose.

A median of 6 (range, 1–14) procedures were performed per patient. Thirty-two percent of patients had a complete ($n = 2$) or partial response ($n = 8$), and 32% of patients achieved stable disease. The median overall survival following treatment was 14.4 months with a 1-year survival of 62%. The median overall survival for patients who responded to treatment was 33.7 months and the median overall survival for patients with stable or progressive disease was 12.4 months. Progression of extrahepatic disease occurred at a median of 10.4 months. In two out of six patients, significant inflammation was found in resected remote extrahepatic metastases. Treatments were well tolerated with symptoms of mild postembolization syndrome. A maximum tolerated dose was not determined in this Phase I trial.

A subsequent analysis compared a similar group of patients treated with chemoembolization using 1,3-bis (2-chloroethyl)-1-nitrosourea (BCNU) to those treated with immunoembolization with either high-dose GM-CSF ($\geq$1,500 μg) or low-dose GM-CSF ($<$ 1,500 μg).[28] Patients treated with immunoembolization using high-dose GM-CSF had a significantly longer median overall survival compared with patients treated with BCNU chemoembolization (20.4 vs. 9.8 months; $p = 0.005$). However, there was no significant difference in overall survival for patients treated with low-dose immunoembolization compared with those treated with BCNU chemoembolization. In addition, there was a significantly longer progression-free survival from extrahepatic metastases in patients treated with high-dose immunoembolization compared with those treated with chemoembolization (12.4 vs. 4.8 months; $p = 0.001$). A delay in onset or progression of extrahepatic metastases was also detected in the high-dose immunoembolization group compared with the low-dose immunoembolization group (12.4 vs. 5.6 months; $p = 0.007$). Based on these results, stabilization of hepatic metastases was likely achieved in the low-dose immunoembolization group by the ischemic effects of recurrent embolization and not from the administration of GM-CSF. In addition, the delay in extrahepatic progression in the high-dose immunoembolization group suggested the induction of a systemic immune response against uveal melanoma cells stimulated by the immunomodulator.

Based on these encouraging results, our institution conducted a randomized, double-blind Phase II (2005–2010) clinical trial comparing immunoembolization to bland embolization.[29] Fifty-two patients were treated using either 2,000 μg of GM-CSF or saline emulsified in ethiodized oil followed by gelatin sponge embolization. This study was specifically designed to compare immunologic outcomes. Peripheral blood specimens were drawn to determine GM-CSF and cytokine levels before and at two time points postprocedure. Treatment and follow-up were the same as previously described for our Phase I trial, but the presence of extrahepatic metastasis excluded patients from enrollment. Patients were stratified based on a hepatic tumor burden of $<$ 20% or 20 to 50%. Overall median survival was 21.5 months for patients undergoing immunoembolization compared with 17.2 months for those treated with bland embolization. In patients with 20 to 50% hepatic tumor burden, there was a significant difference in median overall survival of 18.2 months for those treated with immunoembolization compared with 16.0 months for those treated with bland embolization ($p = 0.047$). A trend toward a delay in the development of extrahepatic metastases was observed in the immunoembolization group (10.4 months) compared with patients in the bland embolization (7.1 months) group. All patients eventually developed progression of hepatic metastases. There were no complete responses in either group. A partial response was seen in 21.2% of patients in the immunoembolization group and 16.7% of patients in the bland embolization group. Unexpectedly, for patients with less than 20% hepatic tumor burden, 28% in the immunoembolization group versus 7% in the bland embolization group experienced progression of disease as their best radiologic response. We hypothesized that high-dose GM-CSF caused a paradoxical response in patients with limited tumor burden within the liver. Since patients with extrahepatic disease were excluded from this trial, we had a contemporaneous comparison group of patients treated under a modified immunoembolization protocol using 1,500 μg of GM-CSF.[30] A retrospective analysis of this patient population revealed that the time to hepatic tumor progression and overall survival were both improved in patients with $<$ 20% tumor burden compared with our Phase II trial.[25] Therefore,

1,500 µg of GM-CSF remains our standard dose currently used for patients undergoing immunoembolization.

Our Phase II study was not powered to determine survival benefit but rather it was designed to investigate the hypothesis that embolization with GM-CSF would enhance the release of proinflammatory cytokines and delay the development of extrahepatic metastases.[29] In patients treated with bland embolization, a significant elevation in levels of interleukin (IL)-6 and IL-8 was identified 18 hours postprocedure. In patients treated with immunoembolization, a rapid increase in tumor necrosis factor-α, IL-6, and IL-8 was detected within an hour post-procedure, suggesting a faster and stronger inflammatory response compared with patients treated with bland embolization, along with a continued increase in IL-6 and IL-8 levels 18 hours postprocedure. Furthermore, an increased IL-6 level at 1 hour and an increased IL-8 level at 18 hours postprocedure correlated with a delay in onset of extrahepatic metastases in a dose–response pattern.

Despite the aggressive nature of this disease, a subset of patients may experience a prolonged survival. A retrospective analysis of 174 patients initially treated with immunoembolization showed that 16, 11, and 5% of patients survived more than 3, 4, and 6 years, respectively.[31] Unfortunately, we are currently unable to prospectively determine which patients will achieve this long-term benefit. However, patients with SF3B1-mutated tumors may have a better prognosis and a prolonged survival compared with patients without this tumor mutation, but further investigation is required.[32]

Indications and Contraindications

Patients with uveal melanoma typically present with multiple tumors in both lobes of the liver when metastatic disease is diagnosed. Immunoembolization is our preferred treatment of choice for patients with limited hepatic tumor burden, multiple small hepatic metastases ($<$ 1–2 cm), and minimal extrahepatic disease. Occasionally, patients will present with oligometastatic disease defined as less than three hepatic tumors. Ablation or surgical resection may be considered under these circumstances depending on the length of time between the primary eye tumor diagnosis and confirmation of metastatic disease. In the surgical literature, ablation or surgical resection is favored for patients with oligometastatic disease that develops more than 5 years from initial eye tumor diagnosis.[33–35] We similarly follow these guidelines since this typically corresponds with a more indolent tumor biology and a higher likelihood of achieving a prolonged period of "no active disease" following surgery or ablation. In our experience, immunoembolization is less effective for patients with hepatic tumor burdens greater than 50% or with liver metastases measuring greater than 5 to 6 cm. Chemoembolization, which administers a cytotoxic agent that destroys hepatic tumors, is a more appropriate treatment option for patients presenting with extensive tumor burden within the liver. At our institution, BCNU chemoembolization is the treatment of choice for these particular patients.[14] On the other hand, we will perform immunoembolization for patients with 20 to 50% tumor burden especially if there is a delay between the primary eye tumor diagnosis and the development of metastatic disease akin to the guidelines used for ablation and surgical resection.

Intravenous or oral steroid administration is contraindicated for patients undergoing immunoembolization since this could hinder the intended immune augmentation. Therefore, carbon dioxide or gadolinium is used as intravascular contrast agents for patients with allergies to iodinated contrast that require steroid preparation. Similarly, patients with immune disorders that require chronic steroid therapy should not be treated with immunoembolization.

Toxicity and Adverse Reactions

As previously mentioned, immunoembolization is typically very well-tolerated. Patients may occasionally experience transient hypotension and/or bradycardia shortly after immunoembolization which is treated with intravenous fluids and, rarely, intravenous atropine. It is common for patients to experience mild post-embolization syndrome, and mild flu-like symptoms related to the administration of GM-CSF. Vascular leak syndrome, a side-effect of immunotherapy, is exceedingly rare after immunoembolization. Vascular leak syndrome is characterized by a massive leakage of plasma from capillaries producing hypotension, diffuse edema, and organ failure. Of note, vascular leak syndrome or serious adverse events were not encountered in either of our Phase I or Phase II clinical trials. Despite the rare occurrence of serious adverse events, we typically observe patients overnight following the first couple of treatments to monitor for and manage symptoms related to the procedure. However, if patients tolerate their initial treatments well, they are often discharged the same day following subsequent immunoembolization procedures.

Immunoembolization and Systemic Therapy

Over the past several years, multiple systemic therapies have been developed to treat a variety of cancer types. Immune checkpoint inhibitors or blockades are agents that remove inhibitory signals of T-cell activation, giving tumor-reactive T-cells the ability to overcome regulatory mechanisms and mount an effective response against tumors. Unfortunately, and dissimilar to cutaneous melanoma, multiple small trials and retrospective reviews have shown poor response rates (3–17%) using immune checkpoint inhibitors to treat metastatic uveal melanoma.[36–39] Therefore, our institution sought to enhance the systemic effects of both immune checkpoint inhibitors and immunoembolization by supplementing immunoembolization with ipilimumab (anti-CTLA-4) alone or in combination with nivolumab (anti-PD-1). In a retrospective review, 27 patients with metastatic uveal melanoma underwent treatment with ipilimumab either right before or contemporaneously with initiation of immunoembolization.[40] The median survival in this group of patients was 20.1 months. Unfortunately, the addition of ipilimumab did not prevent the spread of extrahepatic disease as intended. In fact, 89% of the 18 patients without extrahepatic metastases at

the start of treatment eventually developed systemic disease. Although it appears that it is safe to use ipilimumab with immunoembolization, patients often experienced typical and well-known toxicities associated with ipilimumab therapy that we have not seen with immunoembolization alone. Based on this experience, we subsequently conducted a prospective clinical trial evaluating the use of ipilimumab and nivolumab along with immunoembolization. Due to severe toxicities associated with this combination therapy, the trial was terminated prematurely. It is important to note that while steroid administration should be avoided in patients treated with immunoembolization, side effects and toxicities commonly seen with immune checkpoint inhibitors often require treatment with steroids, thereby delaying and suppressing the immunologic effects of immunoembolization.

Recently, a class of drug known as immune-mobilizing monoclonal T-cell receptors against cancer (ImmTACs) has been FDA-approved for the treatment of metastatic uveal melanoma. Tebentafusp or KIMMTRAK (Immunocore, Ltd) marks a new systemic treatment strategy, whereby the drug serves as a "magnet" pulling T-cells to the melanoma cells.[41] This helps solve the adeptness of melanoma cells to successfully evade immune surveillance. Tebentafusp is typically administered weekly and requires a certain tissue type (human leukocyte antigen-0201–restricted gp100 peptide), present in ~50% of the Caucasian population, to be effective. In both the first in-human and phase I study for metastatic uveal melanoma, tebentafusp demonstrated promising results with a disease control rate of 71% and durable disease control rate of 41%.[42] Progression-free survival was 6 months, and 1-year overall survival was 75%. Additionally, the adverse event profile is much more favorable than that of immune check point inhibitors. Our institution is currently implementing a clinical trial to investigate the feasibility, safety, and efficacy of combining immunoembolization with tebentafusp to treat patients with this aggressive disease.

Imaging Surveillance

Patients diagnosed with uveal melanoma require imaging surveillance given that ~50% of patients develop metastatic disease despite successful treatment of the primary eye tumor. Abdominal MRI at 1.5 or 3 Tesla is the modality of choice with the highest sensitivity for detecting uveal melanoma hepatic metastases. Contrast-enhanced MRI using gadoxetate disodium or Eovist (Bayer Healthcare, Whippany, NJ) is superior to CT in the detection of small hepatic metastases. On delayed phase imaging, also known as the hepatobiliary phase, metastases unlike normal functioning hepatocytes do not retain Eovist and essentially appear as "holes" in the liver parenchyma making them more conspicuous on MRI compared with other contrast agents (►**Fig. 2**).[42] Diffusion-weighted sequences are also remarkably sensitive in depicting melanoma metastases and should be included as part of the MRI exam (►**Fig. 3**).[43] Although MRI is superior for detecting metastatic disease, CT imaging is important for the detection of extrahepatic disease including but not limited to pulmonary, osseous, and peritoneal metastases.

Based on the rapid growth that may be seen with this disease, we suggest that an MRI be obtained shortly before starting treatment to provide a contemporaneous baseline.

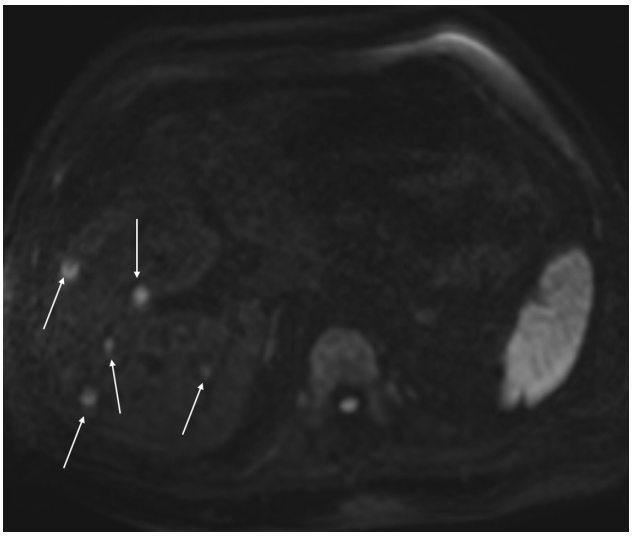

Fig. 3 Uveal melanoma metastases (arrows) appear bright on MRI diffusion-weighted imaging.

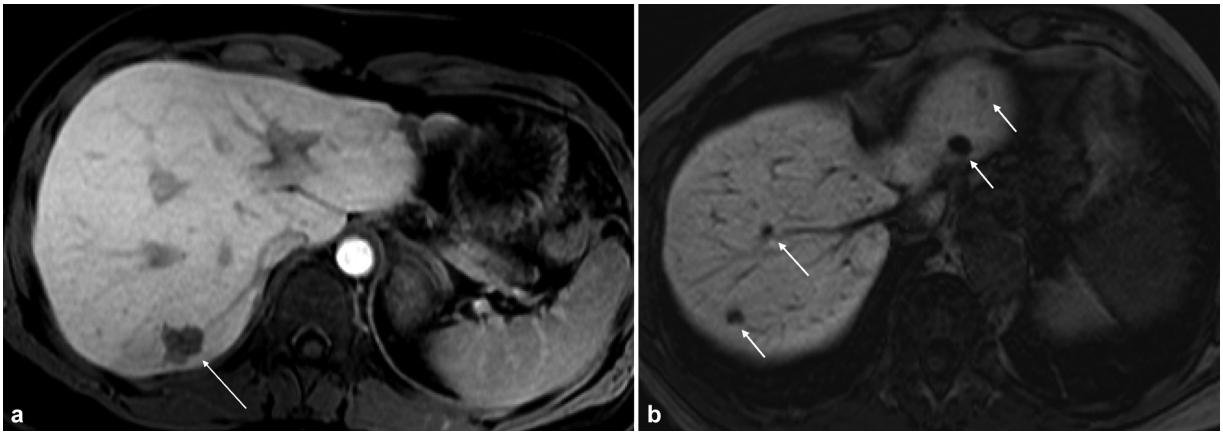

Fig. 2 (**a** and **b**) Contrast-enhanced MRI with gadoxetate disodium (Eovist). Multiple metastatic uveal melanomas (arrows) appear as "holes" in the liver on delayed phase or hepatobiliary phase imaging.

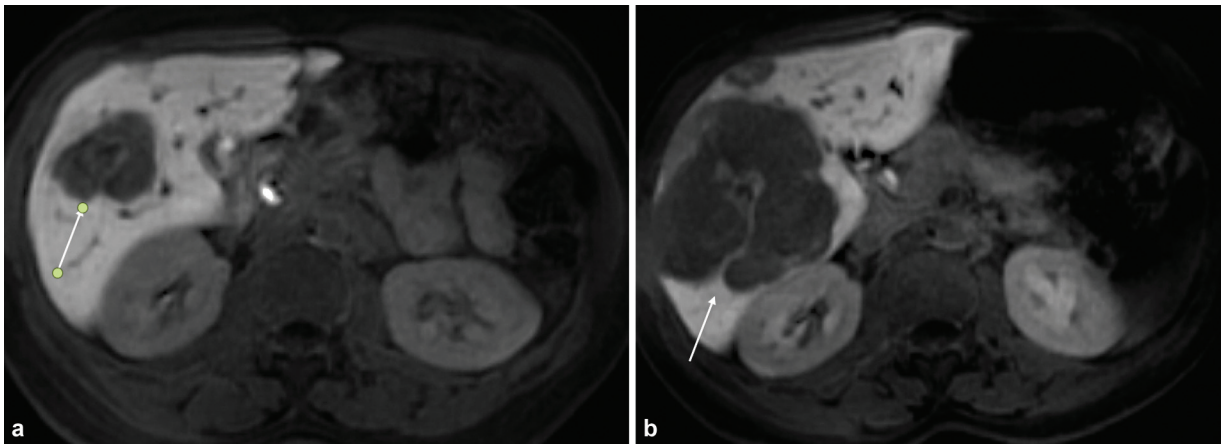

Fig. 4 (**a**) Large tumor (arrow) in the right lobe of the liver identified on contrast-enhanced MRI. (**b**) Rapid progression of untreated metastatic uveal melanoma on repeat MRI performed 4 weeks later demonstrating the aggressive nature of this disease and the rationale for contemporaneous imaging prior to treatment.

While imaging within 4 weeks of starting treatment is acceptable, 2 weeks is often preferable based on the aggressive nature of this disease (►**Fig. 4**).

Conclusion

Immunoembolization for the treatment of uveal melanoma hepatic metastases is beneficial to prolonging survival for patients with this aggressive disease. Immunoembolization is our mainstay treatment for patients presenting with limited hepatic tumor burden because it is well tolerated, has limited side-effects, no cumulative toxicities, and affords good quality of life between scheduled treatments. The benefit of adding tebentafusp to liver-directed treatment is still unknown. However, as previously mentioned, we are currently implementing a clinical trial combining immunoembolization and tebentafusp with the hopes of delaying the progression of both hepatic and extrahepatic disease, thus prolonging the overall survival of patients with metastatic uveal melanoma.

References

1 Aronow ME, Topham AK, Singh AD. Uveal melanoma: 5-year update on incidence, treatment, and survival (SEER 1973–2013). Ocul Oncol Pathol 2018;4(03):145–151
2 Kaliki S, Shields CL. Uveal melanoma: relatively rare but deadly cancer. Eye (Lond) 2017;31(02):241–257
3 Shields CL, Shields JA. Ocular melanoma: relatively rare but requiring respect. Clin Dermatol 2009;27(01):122–133
4 Ulmer A, Beutel J, Süsskind D, et al. Visualization of circulating melanoma cells in peripheral blood of patients with primary uveal melanoma. Clin Cancer Res 2008;14(14):4469–4474
5 Krantz BA, Dave N, Komatsubara KM, Marr BP, Carvajal RD. Uveal melanoma: epidemiology, etiology, and treatment of primary disease. Clin Ophthalmol 2017;11:279–289
6 Yang J, Manson DK, Marr BP, Carvajal RD. Treatment of uveal melanoma: where are we now? Ther Adv Med Oncol 2018; 10:1758834018757175
7 van den Bosch T, van Beek JGM, Vaarwater J, et al. Higher percentage of FISH-determined monosomy 3 and 8q amplification in uveal melanoma cells relate to poor patient prognosis. Invest Ophthalmol Vis Sci 2012;53(06):2668–2674
8 Cassoux N, Rodrigues MJ, Plancher C, et al. Genome-wide profiling is a clinically relevant and affordable prognostic test in posterior uveal melanoma. Br J Ophthalmol 2014;98(06):769–774
9 Onken MD, Worley LA, Char DH, et al. Collaborative Ocular Oncology Group report number 1: prospective validation of a multi-gene prognostic assay in uveal melanoma. Ophthalmology 2012;119(08):1596–1603
10 Field MG, Decatur CL, Kurtenbach S, et al. PRAME as an independent biomarker for metastasis in uveal melanoma. Clin Cancer Res 2016;22(05):1234–1242
11 Sato T. Locoregional management of hepatic metastasis from primary uveal melanoma. Semin Oncol 2010;37(02):127–138
12 Spagnolo F, Caltabiano G, Queirolo P. Uveal melanoma. Cancer Treat Rev 2012;38(05):549–553
13 Patel K, Sullivan K, Berd D, et al. Chemoembolization of the hepatic artery with BCNU for metastatic uveal melanoma: results of a phase II study. Melanoma Res 2005;15(04):297–304
14 Gonsalves CF, Eschelman DJ, Thornburg B, Frangos A, Sato T. Uveal melanoma metastatic to the liver: chemoembolization with 1,3-bis-(2-Chloroethyl)-1-nitrosourea. AJR Am J Roentgenol 2015; 205(02):429–433
15 Vogl T, Eichler K, Zangos S, et al. Preliminary experience with transarterial chemoembolization (TACE) in liver metastases of uveal malignant melanoma: local tumor control and survival. J Cancer Res Clin Oncol 2007;133(03):177–184
16 Gonsalves CF, Eschelman DJ, Sullivan KL, Anne PR, Doyle L, Sato T. Radioembolization as salvage therapy for hepatic metastasis of uveal melanoma: a single-institution experience. AJR Am J Roentgenol 2011;196(02):468–473
17 Klingenstein A, Haug AR, Zech CJ, Schaller UC. Radioembolization as locoregional therapy of hepatic metastases in uveal melanoma patients. Cardiovasc Intervent Radiol 2013;36(01):158–165
18 Eldredge-Hindy H, Ohri N, Anne PR, et al. Yttrium-90 microsphere brachytherapy for liver metastases from uveal melanoma: clinical outcomes and the predictive value of fluorodeoxyglucose positron emission tomography. Am J Clin Oncol 2016;39(02):189–195
19 Gonsalves CF, Eschelman DJ, Adamo RD, et al. A prospective phase II trial of radioembolization for treatment of uveal melanoma hepatic metastasis. Radiology 2019;293(01):223–231
20 Hughes MS, Zager J, Faries M, et al. Results of a randomized controlled multicenter phase III trial of percutaneous hepatic perfusion compared with best available care for patients with melanoma liver metastases. Ann Surg Oncol 2016;23(04):1309–1319
21 Kanai T, Monden M, Sakon M, et al. New development of transarterial immunoembolization (TIE) for therapy of hepatocellular

carcinoma with intrahepatic metastases. Cancer Chemother Pharmacol 1994;33(Suppl):S48–S54
22 Yoshida T, Sakon M, Umeshita K, et al. Appraisal of transarterial immunoembolization for hepatocellular carcinoma: a clinicopathologic study. J Clin Gastroenterol 2001;32(01):59–65
23 Saito T, Tsuchiya T, Sato Y, et al. Effect of transarterial immunoembolization as preoperative treatment for hepatocellular carcinoma. Ann Cancer Res Therap 2011;19:26–33
24 Nakamoto Y, Mizukoshi E, Kitahara M, et al. Prolonged recurrence-free survival following OK432-stimulated dendritic cell transfer into hepatocellular carcinoma during transarterial embolization. Clin Exp Immunol 2011;163(02):165–177
25 Dranoff G, Jaffee E, Lazenby A, et al. Vaccination with irradiated tumor cells engineered to secrete murine granulocyte-macrophage colony-stimulating factor stimulates potent, specific, and long-lasting anti-tumor immunity. Proc Natl Acad Sci U S A 1993; 90(08):3539–3543
26 Sullivan KL, Aoyama T, Sato T, McCue P. Safety of immunoembolization of normal swine liver with human GM-CSF (granulocyte macrophage colony stimulating factor) and ethiodol. J Vasc Interv Radiol 2001;12:S132–S133
27 Sato T, Eschelman DJ, Gonsalves CF, et al. Immunoembolization of malignant liver tumors, including uveal melanoma, using granulocyte-macrophage colony-stimulating factor. J Clin Oncol 2008; 26(33):5436–5442
28 Yamamoto A, Chervoneva I, Sullivan KL, et al. High-dose immunoembolization: survival benefit in patients with hepatic metastases from uveal melanoma. Radiology 2009;252(01): 290–298
29 Valsecchi ME, Terai M, Eschelman DJ, et al. Double-blinded, randomized phase II study using embolization with or without granulocyte-macrophage colony-stimulating factor in uveal melanoma with hepatic metastases. J Vasc Interv Radiol 2015; 26(04):523–32.e2
30 Gutjahr CJ, Gonsalves CF, Eschelman DJ, Frangos A, Meshekow JS, Sato T. Immunoembolization (IE) using 1500 mcg of granulocyte macrophage-colony stimulating factor (GM-CSF) and 2 million IU of interleukin-2 (IL-2) for the treatment of uveal melanoma (UM) hepatic metastases. J Vasc Interv Radiol 2014;25:S26
31 Ford R, Gonsalves C, Adamo R, et al. Prolonged survival after treatment of hepatic uveal melanoma metastases using immunoembolization. J Vasc Interv Radiol 2019;30:S140
32 Seedor RS, Orloff M, Sato T. Genetic landscape and emerging therapies in uveal melanoma. Cancers (Basel) 2021;13(21):5503
33 Aoyama T, Mastrangelo MJ, Berd D, et al. Protracted survival after resection of metastatic uveal melanoma. Cancer 2000;89(07): 1561–1568
34 Akyuz M, Yazici P, Dural C, et al. Laparoscopic management of liver metastases from uveal melanoma. Surg Endosc 2016;30(06): 2567–2571
35 Mariani P, Almubarak MM, Kollen M, et al. Radiofrequency ablation and surgical resection of liver metastases from uveal melanoma. Eur J Surg Oncol 2016;42(05):706–712
36 Zimmer L, Vaubel J, Mohr P, et al. Phase II DeCOG-study of ipilimumab in pretreated and treatment-naïve patients with metastatic uveal melanoma. PLoS One 2015;10(03):e0118564
37 Heppt MV, Heinzerling L, Kähler KC, et al. Prognostic factors and outcomes in metastatic uveal melanoma treated with programmed cell death-1 or combined PD-1/cytotoxic T-lymphocyte antigen-4 inhibition. Eur J Cancer 2017;82:56–65
38 Algazi AP, Tsai KK, Shoushtari AN, et al. Clinical outcomes in metastatic uveal melanoma treated with PD-1 and PD-L1 antibodies. Cancer 2016;122(21):3344–3353
39 Piulats Rodriguez JM, De La Cruz Merino L, Espinosa E, et al. Phase II multicenter, single arm, open label study of nivolumab in combination with Ipilimumab in untreated patients with metastatic uveal melanoma. Ann Oncol 2018;29:442–466
40 Guez D, Eschelman D, Pan K, et al. Ipilimumab combined with immunoembolization for treatment of uveal melanoma metastatic to the liver. J Vasc Radiol 2019;30:S141
41 Sato T, Nathan PD, Hernandez-Aya L, et al. Redirected T cell lysis in patients with metastatic uveal melanoma with gp100-directed TCR IMCgp100: overall survival findings. J Clin Oncol 2018;36:9521
42 Carvajal RD, Sacco J, Nathan P, et al. Safety, efficacy and biology of the gp100 TCR-based bispecific T cell redirector IMCgp100 in advanced uveal melanoma. Invest Ophthalmol Vis Sci 2018;59:3622
43 Balasubramanya R, Selvarajan SK, Cox M, et al. Imaging of ocular melanoma metastasis. Br J Radiol 2016;89(1065):20160092