Percutaneous hepatic perfusion with melphalan for metastatic uveal melanoma: mounting evidence and future perspectives

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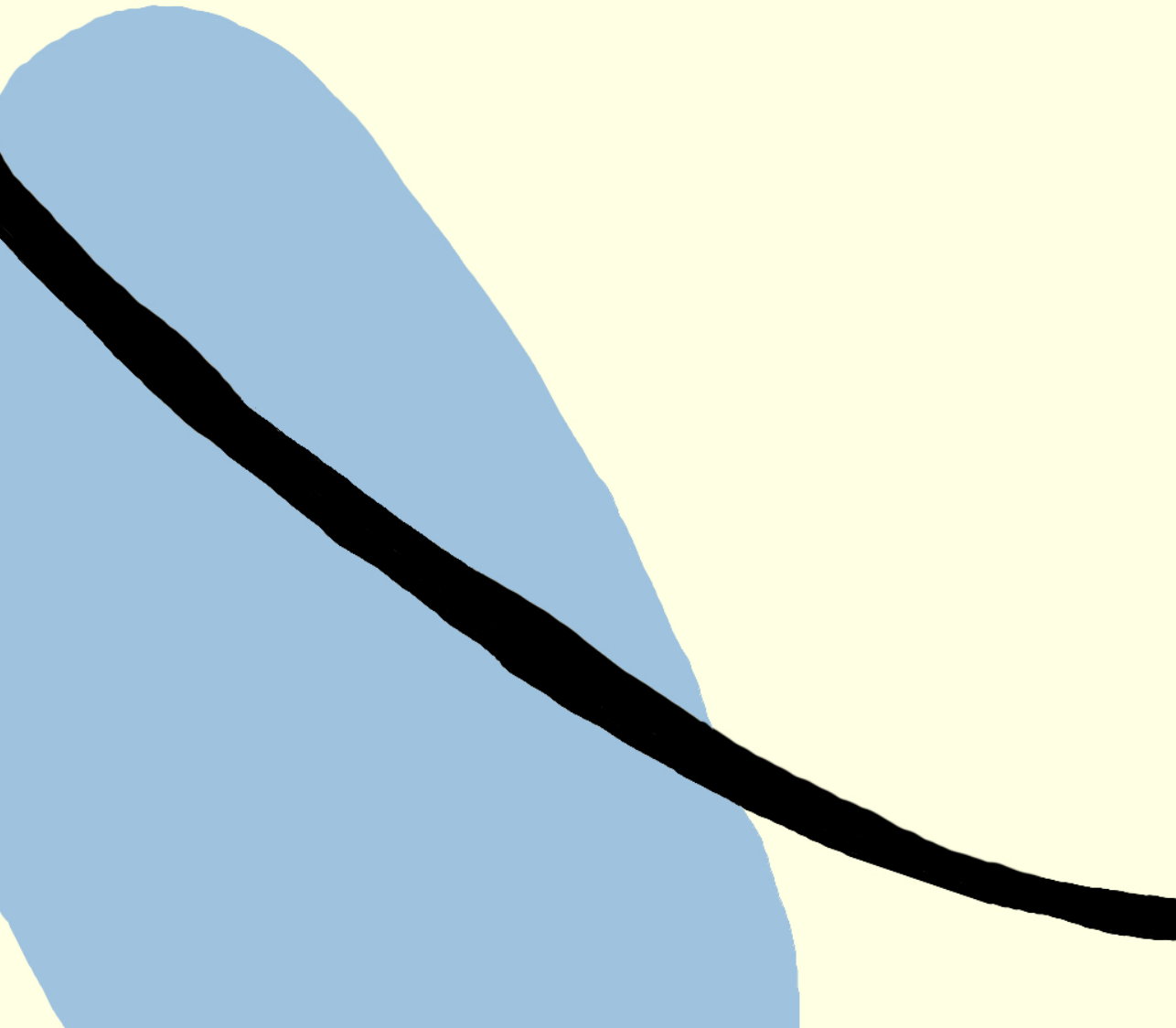
Chapter 1



GENERAL INTRODUCTION AND THESIS OUTLINE

Background

Uveal Melanoma (UM) is an uncommon malignancy originating from melanocytes in the uveal tract of the eye. It has an incidence number of 4.4 patients per million per year in Europe (1). Despite the low incidence, it is the most common primary ocular tumor in adults and accounts for 5% of all deaths due to melanoma (2, 3). The tumor arises in the uveal tract of the eye, specifically the choroid (in up to 90% of patients), the ciliary body (6% of cases) or the iris (4% of cases) (4). Symptoms are related to the tumor location and can include blurred vision, photopsia, visual field loss, or decreased visual acuity due to secondary retinal detachment (5). However, many patients are asymptomatic and get diagnosed upon routine eye investigations for reasons unrelated to the tumor.

Treatment options for the primary tumor are with curative intent and consist of surgical removal of the eye (enucleation) or radiotherapy (6). The treatment decision depends on the tumor location, size (diameter and prominence), involvement of the ciliary body or iris and proximity to the optic disc (7). Age, comorbidities and patient preference also play a role. Enucleation is the standard treatment option in patients with large UMs, defined as tumors larger than 16mm in basal diameter or more than 10mm in height (8). Benefits of enucleation include that it allows for pathological assessment of the entire tumor, which is important for determining the definitive tumor size, characteristics, stage, and metastatic risk. Furthermore, it provides rapid and definitive relief from symptoms that patients might have been experiencing. However, surgical removal of the eyeball results in permanent loss of the eye and vision, with significant psychological impact and functional impairment. Patients will have to adjust to the use of a prosthetic eye and monocular vision.

Contrary to enucleation, treatment with radiotherapy preserves the eye. The most frequently used types of radiotherapy include brachytherapy (Ruthenium and Iodine) and proton beam therapy. Brachytherapy is used for small and medium-sized tumors (up to 16mm in basal diameter and 7mm thickness), while proton therapy is often the treatment choice in case of larger or juxtapupillary tumors (9). Just like with enucleation, radiotherapy is performed as a treatment with curative intent. Depending on the location of the tumor, vision and visual acuity may be preserved. Larger tumors lead to a higher chance of vision loss or radiotherapy-related complications (10), which is why these are rarely treated with eye-

preserving modalities. Local tumor control depends on the treatment modality and ranges between 95-98% (11). Local recurrence rates after radiation therapy is between 0-22%, and this ranges between 1-10% for iodine-125 and ruthenium-106 (12). In general, globe-sparing treatments have become more popular in recent years, since it was demonstrated that there is no difference in survival rates between patients treated with brachytherapy compares to enucleation (13).

Despite successful treatment of the primary tumor, the long-term prognosis for patients with metastatic disease remains dismal. The cumulative chance of developing metastases is 25% within 5 years, and 34% within 10 years (14). The main predictors of UM-related death include tumor stage, genetic mutations, largest basal diameter, extraocular growth and ciliary body involvement (15). Tumors located more anteriorly, specifically in the ciliary body, are associated with the worst prognosis. The 10-year rates for metastatic disease in a large study was 33% for ciliary body tumors, as compared to 7 and 25% for iris- and choroidal melanoma respectively (4). Early identification of the tumor is key, since a higher tumor stage according to the American Joint Committee on Cancer (AJCC) at the moment of diagnosis, is also related to a higher chance of mortality due to metastatic disease (4, 14). The higher the stage, the more mutant cells have accumulated. Finally, monosomy of chromosome 3 and 8q gain are notoriously associated with worse survival. Once metastases occur, the mortality rate is 80% after 1 year and 92% after 2 years (14), and there has been little improvement in prognosis. For this reason, the challenge remains to find better treatment options to achieve disease control and improve survival of patients presenting with metastatic UM.

Biological Characteristics

UM is characterized by a low mutational burden, making it in essence an immunologically 'cold' tumor. There are specific oncogenic mutations and chromosomal copy number aberrations that occur with UM, including gain of chromosomes 1q, 3, 6p and 8q and loss of chromosomes 1p, 3, 6q, 8p (16). Particularly, 8q gain and chromosome 3 monosomy occur early, while other alterations occur later in the UM pathogenesis (17) and are related to survival. The initiating mutation most often consists of either GNAQ or GNA11 mutation (18). Other key driver genes in the development of UM are BAP1, EIF1AX and SF3B1 (17). The precursor cells after the initiating phase

can have either chromosome 3 disomy (65%) or monosomy (35%). Tumors harboring disomy 3 are associated with mutations in EIFA1X or SF3B1, and have a more favorable prognosis. If disomy-3 tumors present with gains of chromosome 6p, partial gains of chromosome 8q, and/or mutations in SF3B1, they are related to higher metastatic rates (Categories 1A vs 1B) (18). Tumors with monosomy of chromosome 3 are frequently related to loss of BAP1. Metastatic risk increases if there is both BAP1 loss and chromosome 8q gains (19).

Metastatic UM

Aside from the biological characteristics, UM distinguishes itself from other melanoma types by the hematogenous metastatic pattern. The liver will be the primary location of metastases in up to 90% of patients (20). Metastatic tumor growth and resulting liver failure is the main cause of mortality. The liver is characterized by an immunosuppressive environment making it more inhabitable for UM metastases, and thus challenging to treat the metastases (19). Furthermore, the metastatic pattern could possibly also be explained by the expression of Hepatocyte Growth Factor (HCG) in the liver. HCG is a ligand of cMET, which is expressed by UM cells (21, 22). The ligand CXCR12 is also produced by the hepatic sinusoidal endothelial cells and the hepatic stellate cells, which is a ligand for factor CXCR4 expressed in UM. These could play a role in tumor dissemination (6). Due to aforementioned reasons, there will be regular follow-ups after treatment for the primary tumor.

The Dutch guidelines on UM recommend routine follow-up abdominal ultrasounds every 6 months after diagnosis of the primary tumor, for 10 years in total, in accordance with the UK national guidelines (23). Once metastases are detected, either liver-directed therapies or systemic treatments can be considered. Treatment choice is made based on several clinical factors, such as the liver tumor burden, presence of extrahepatic disease, patient comorbidity and fitness. If there is evident extrahepatic disease patients are eligible for systemic treatment, while liver-directed treatments are reserved for those with metastases confined to the liver. In the following paragraphs, a short overview will be given of past and currently investigated treatment options for hepatic metastases from UM.

Liver-directed therapies

Considering the metastatic pattern of UM, local treatment options directed on the liver play a key role in treatment. The available options consist of either surgically removing the tumor, or approaching the tumor transarterially by the interventional radiologist. With transarterial approaches, the goal is to optimize the delivery of therapeutic agents directly to the tumor, while minimizing damage to the healthy liver tissue and minimizing systemic exposure. Several techniques have been used and investigated in the past years. Hepatic neoplasms are predominantly supplied by the hepatic artery, while healthy liver tissues derive the majority of their blood supply from the portal vein. Transarterial therapies make use of this difference in blood supply, by selectively delivering medication through the hepatic artery (24). Thereby making it possible to selectively target liver tumors and deliver therapeutic agents locally with minimal systemic exposure. These options are explained in the following paragraphs.

Surgical resection and thermal ablation

Metastasectomy and thermal ablation (radiofrequency or microwave ablation) of liver metastases provide the longest overall survival (OS) and can potentially be curative for a group of patients. Those with small (<3 cm) and a limited number (1-3) of liver metastases are eligible for these treatment options. Unfortunately, less than 10% of metastatic patients are suitable candidates for resection or ablation, often because diffuse, bilobar liver lesions are already present at the moment of diagnosis of metastasized disease (25).

Transarterial chemo-embolization

With transarterial chemoembolization (TACE) microparticles loaded with a chemotherapeutic agent are administered percutaneously through the hepatic artery. These particles occlude the blood vessel and provide a slow, local release of chemotherapy. Studies show a wide range of median OS between 6 and 28.7 months (26). However, these studies are very heterogenous due to a difference in the used chemotherapy, patient population and treatment protocol. In general a lower tumor load in the liver corresponds with better outcomes (25, 26).

Transarterial radio-embolization

In transarterial radioembolization (TARE), particles labeled with Yttrium-90 or Holmium-166 are administered percutaneously through the hepatic artery. These particles settle in the terminal arterioles of the tumor's microvasculature and deliver local radiation there. This allows for the administration of a high dose of radiotherapy to the metastases with limited toxicity to the surrounding healthy liver parenchyma. This technique is mostly used as palliative therapy in patients with progressive disease after previous treatments (26). In a retrospective study, patients with a tumor load of <25% in the liver achieved a longer OS compared to patients with >25% affected liver parenchyma (27).

Percutaneous hepatic perfusion with melphalan

Percutaneous hepatic perfusion with melphalan (M-PHP) is a minimally invasive procedure to provide a high dose of melphalan specifically to the liver. Systemic melphalan exposure is limited by isolating the liver from the rest of the circulation with two balloons, one at the atrio-caval junction and the other one in the inferior vena cava. Prior to the introduction of M-PHP, isolated hepatic perfusions (IHP) were performed, which is the surgical counterpart of M-PHP (28). Treatment with IHP results in a superior overall response rate (ORR), progression-free survival (PFS) and hepatic PFS compared to investigator's choice of treatment according the results of a randomized, phase III trial (SCANDIUM) (29). Nonetheless, a meta-analysis conducted by Bethlehem et al reveals a significantly elevated risk of complications and mortalities associated with IHP, in comparison to M-PHP (30). Furthermore, M-PHP has the additional advantages of being a shorter, repeatable procedure, with a shorter recovery time for patients. Accumulating evidence in favor of M-PHP has been observed in recent years. Preliminary results of a recent phase III trial (FOCUS) investigating M-PHP compared to best alternative care (BAC) showed a significantly improved PFS and OS in patients treated with M-PHP compared to BAC (31). Previous randomized trials, retrospective analyses, and prospective cohort studies have demonstrated the safety and efficacy of M-PHP. The observed adverse events have been predominantly transient and self-limiting (32-37). The mounting evidence has led to the recent approval by the U.S. Food and Drug Administration (FDA) of M-PHP as a treatment for patients with unresectable UM liver metastases. An overview of ongoing trials investigating liver-directed treatments is found in Table 1.

Table 1. Overview of ongoing liver-directed therapy trials

Clinical Trials	Phase	Trial ID
Percutaneous Hepatic Perfusion with Melphalan	EAP	NCT05022901
Intrahepatic Delivery of SD-101 by Pressure-Enabled Regional Immuno-oncology (PERIO), With Checkpoint Blockade in Adults With Metastatic Uveal Melanoma	I/II	NCT04935229
M-PHP with Immunotherapy (IPI/NIVO) in Metastasized UM (CHOPIN)	II	NCT04283890
A Study of Concurrent Stereotactic Body Radiotherapy With Ipi and Nivo in Metastatic Uveal Melanoma	II	NCT05077280
Transarterial Chemoembolization for the Treatment of Uveal Melanoma With Liver Metastases	II	NCT04728633
Isolated Hepatic Perfusion in Combination With Ipilimumab and Nivolumab in Patients With Uveal Melanoma Metastases (SCANDIUM II)	I	NCT04463368

Systemic Therapies

Chemotherapy

UM is notoriously resistant to conventional chemotherapy. Treatment response rates are low and there is no OS gain (10, 38). In a meta-analysis by Rantala et al the cumulative OS of several chemotherapy agents was 10.9 months (39), while Khoja et al. determined a median OS of 10.2 months in their meta-analysis (40). Due to aforementioned reasons, systemic chemotherapy no longer has a role in the treatment of metastatic UM.

Targeted therapy

Recent advancements in understanding the molecular biology of UM has paved the way for the development of several targeted therapies. Targeted therapies aim to disrupt signaling pathways that drive tumor growth by inhibiting specific downstream molecules in these pathways. Examples are the MEK inhibitors and PKC inhibitors. These inhibitors initially showed disappointing results, with response percentages lower than 10% for the PKC inhibitor sotrastaurin (41). A randomized trial with the MEK-inhibitor selumetinib, combined with dacarbazine, showed no PFS gain compared to dacarbazine monotherapy (42). More recent trials investigating targeted therapies are ongoing. Daroversitib (LXS196) seems promising and is

currently being investigated for efficacy (43, 44) and toxicity in a phase 1/2 trial in combination with binimetib and crizotinib, NCT03947385 (45). An overview of ongoing targeted therapy trials is presented in Table 2.

Table 2. Overview of ongoing targeted therapy trials

Clinical Trials	Target	Trial ID
Study of IDE196 in Patients With Solid Tumors Harboring GNAQ/11 Mutations or PRKC Fusions	PKC/MET (GNAQ/ GNA11)	NCT03947385
IDE196 (Darovasertib) in Combination With Crizotinib as First-line Therapy in Metastatic Uveal Melanoma	IDE196, crizotinib	NCT05987332
Binimetinib Plus Belinostat for Subjects With Metastatic Uveal Melanoma	MEK and HDAC	NCT05170334
Phase 1 Study to Determine the MTD, Safety, Tolerability, PK and Preliminary Anti-tumor Effects of LNS8801alone and With Pembrolizumab	GPER	NCT04130516
Efficacy and Safety of Pembrolizumab in Combination With Lenvatinib in Metastatic Uveal MElanoma Patients (PLUME)	VEGF/PD-1	NCT05282901
A Phase I/II Study of DYP688 in Patients With Metastatic Uveal Melanoma and Other GNAQ/11 Mutant Melanomas	GNAQ/GNA11	NCT05415072
IN10018 Monotherapy and Combination Therapy for Metastatic Melanoma	FAK/MEK	NCT04109456

Immunotherapy

Immunotherapy has revolutionized the treatment of cutaneous melanoma in recent years, in particular treatment with immune checkpoint inhibitors (ICI). Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) is a protein receptor found on the surface of T cells, while Programmed cell death protein 1 (PD-1) is a checkpoint receptor expressed on the surface of particularly T cells. Both of these play a crucial role in regulating immune responses by inhibiting T cells. Anti-CTLA-4 and anti-PD-1 agents are monoclonal antibodies designed to block the CTLA-4 and PD-1 receptors respectively. By binding, these antibodies prevent the inhibitory signals and enhance the immune response against UM cells.

However, the response rates of immunotherapy in metastatic UM are considerably lower compared to those in advanced skin melanoma. The low mutational burden of UM in combination with its unique immune

privilege and the tumor's ability to evade immune surveillance, poses challenges for immunotherapeutic interventions. ICIs are currently applied as monotherapy or combination therapy. Combining anti-CTLA-4 with anti-PD1/anti-PD-L1 agents results in higher response rates (46-50), but has limited effect on the OS. Contrary to ICIs, tebentafusp recently transformed the treatment landscape in metastatic UM by being the first agent that demonstrated a prolonged OS for HLA-A201 positive patients with metastatic UM. Tebentafusp, a bispecific molecule that targets glycoprotein 100 has been approved by the FDA as a systemic treatment option for metastatic UM, based on the results from the randomized phase II trial (51). Three-year follow-up of this trial shows continued long-term OS benefit of treatment with tebentafusp (52). Nonetheless, patients who are HLA-A201 negative cannot be treated with this medication, so clinical studies are still necessary for this group of patients. An overview of ongoing trials with immunotherapy is presented in Table 3.

Combining liver-directed with systemic therapies

Combining liver-directed treatments with systemic therapies in UM is a strategy aimed at achieving improved disease control, reducing tumor burden, and potentially improving the efficacy of systemic treatments by increasing neo-antigen presentation and immunological activity. With this dual approach, both hepatic and extrahepatic disease can be treated. ICI is being investigated in combination with liver-directed therapies such as TACE, IHP, M-PHP and intrahepatic delivery of SD-101 (a TLR9 agonist), as mentioned in Table 1. Combining M-PHP with ipilimumab and nivolumab is also a topic of discussion in this thesis.

Table 3. Overview of ongoing trials with immunotherapy

Clinical Trials	Type	Trial ID
A Study of APG-115 in Combination With Pembrolizumab in Patients With Metastatic Melanomas or Advanced Solid Tumors	MDM2 and PD1	NCT03611868
Safety and Efficacy of IMC-F106C as a Single Agent and in Combination With Checkpoint Inhibitors	PRAME	NCT04262466
A Study of Concurrent Stereotactic Body Radiotherapy With Ipi and Nivo in Metastatic Uveal Melanoma	PD1/CTLA4 + XRT	NCT05077280
Adoptive Transfer of Tumor Infiltrating Lymphocytes for Metastatic Uveal Melanoma	TIL	NCT03467516
Phase 1 Study to Determine the MTD, Safety, Tolerability, PK and Preliminary Anti-tumor Effects of LNS8801alone and With Pembrolizumab	GPER	NCT04130516

Thesis Outline

The goal of this thesis is to discuss the role of M-PHP in the treatment of metastatic UM, as well as to discuss the introduction of the novel combination with immunotherapy. In **Chapter 2** we give an overview of the time trends in survival of patients diagnosed with UM in the Netherlands in a large cohort of 5036 patients. We divided the whole cohort of 1989-2019 in two groups belonging to two time periods (1989-2004, 2005-2019), in order to compare demographics, treatment, OS and cancer-specific survival in the older period with the most recent period. **Chapter 3** focusses on the predictive factors for improved survival after M-PHP treatment, based on a cohort of 101 patients from three different centers. In **Chapter 4**, the results are presented of a prospective study on the quality of life of patients treated with M-PHP. In Chapter 5 and 6 the CHOPIN trial is discussed. In this prospective, randomized trial, M-PHP with or without the ICIs ipilimumab and nivolumab is investigated. **Chapter 5** gives an overview of the rationale and study protocol, while **Chapter 6** discusses the results of the phase Ib part of the trial.

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