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Percutaneous Isolated Hepatic Perfusion with Melphalan in Combination with Immunotherapy for Patients with Hepatic Metastasis of Uveal Melanoma

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Abstract

Objective: Percutaneous isolated hepatic perfusion (PIHP) is becoming increasingly important for the treatment of hepatic metastasis of uveal melanoma. However, the best treatment strategy is not yet clear.

Method: We present a case series of seven patients suffering from hepatic metastases of uveal melanoma who received several treatments of PIHP with melphalan, with or without immunotherapy.

Results: Seven patients with hepatically metastasized uveal melanoma (three men, four woman) with an average age of 51 years (range 37–68 years) received two cycles of PIHP at intervals of 4–10 weeks and were then monitored clinically (three patients) or treated with a PD-1 antibody ± ipilimumab (six patients) until disease progression or intolerable toxicity was determined. Two cycles of PIHP controlled the disease for between 3.9 and 15.6 months, resulting in a median hepatic progression-free survival (hPFS) of 7.3 months. A further 1–2 PIHP cycles were then performed, followed by anti-PD1 therapy for two patients, resulting in short-term control of the disease only. Median hPFS until final disease progression (measured from first PIHP until progression despite PIHP) was 15.4 months (Range 3.9–24.9), and overall survival was 16.8 months (Range 4.8–36.0). The first two PIHP cycles in particular were very well tolerated.

Conclusion: Although conclusions from small case series should be drawn with caution, the clinical experiences described provide the first indications that two treatment cycles of PIHP might suffice to control hepatic metastasis of uveal melanoma for several months. Additional immunotherapy might benefit patients after a reduction of tumour load by PIHP. Side effects and treatment risks seem lower with this treatment scheme. Further studies on this topic are warranted.

Keywords: Uveal melanoma; Liver metastases; Percutanous isolated hepatic perfusion; Immunotherapy, PD1-antibody

Introduction

Uveal melanoma is the most common type of malignant primary ocular tumour among adults and accounts for approximately 80% of ocular melanomas and 3–5% of all melanomas. The age-adjusted incidence in the USA is 5.1 cases per million adults and mainly Caucasians are affected [1]. In Europe, the incidence of uveal melanoma declines from north to south and ranges from two to eight cases per million citizens [2]. Approximately half of patients develop metastases within 10 years, most frequently in the liver (89%), lungs (29%) and bones (17%) [1-7]. Median overall survival after metastatic spread is 6–12 months, and only 13% of patients survive for one year. Different systemic chemotherapies (dacarbazine, temozolomide, cisplatin, treosulfan and combinations of these other combinations) have been used for the treatment of uveal melanoma. However, these chemotherapies have no proven benefit for overall survival and have yielded response rates as low as <10% [8]. Improved progression-free survival has been observed for other systemic agents such as mitogen-activated protein-kinase (MEK) inhibitors (trametinib, cobimetinib) and multi-kinase inhibitors (sorafenib) but, again, no overall survival has been found [9,10]. Immunotherapies with immune-checkpoint blockers (CTLA4, PD1, PD-L1 antibodies), which have achieved remarkable effects in relation to cutaneous melanoma, have seldom controlled uveal melanoma, and their use has resulted in a similar overall survival of only 6–10 months [11-13].

Because extensive liver metastases are usually life-limiting, local liver treatments have been used for several decades for the attempted treatment of uveal melanoma metastasis [3,14-20]. The hepatic artery supplies blood to 95% of all liver metastases [21,22]. It is used to deliver drugs for several local treatments, for example transarterial chemoembolization (TACE), hepatic arterial infusion with e.g. fotemustine, isolated hepatic perfusion (IHP) and percutaneous isolated hepatic perfusion (PIHP) [23-26]. The advantage of hepatic perfusion is that it reaches all tumour cells in the liver, not only those detected during tumour assessment by means of e.g. computed tomography (CT). This is particularly important for uveal melanoma because metastasis to the liver is usually widespread and not limited to single metastases. PIHP is performed transvascularly by an interventional radiologist in a specialized team. Because the liver is isolated from the blood cycle for the duration of infusion, a higher concentration of chemotherapeutic agent is used for PIHP than for systemic therapy. In studies on the alkylating agent melphalan, a response has been observed for several types of cancer [23,27-31]. The response for uveal melanoma is as high as 80% [32,33]. PIHP can be repeated and is usually performed every 4–8 weeks. Although the treatment is usually well tolerated, there are

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potential risks for the patient, and it is usually not administered more than six times [34]. Here we present seven patients with metastatic uveal melanoma who received PIHP in a protracted treatment schedule.

Case Series

Clinical data from seven patients who repeatedly received PIHP between 2012 and 2019 for the treatment of liver metastasis of uveal melanoma were retrospectively analysed. PIHP was performed as has been previously reported [34]. Briefly, an arteriogram is performed first to embolize the gastroduodenal artery and other accessory vessels if necessary. Then, a catheter is placed to deliver melphalan directly into the hepatic artery. To protect other organs, a double-balloon catheter is positioned in the inferior vena cava (IVC), usually via the right femoral vein. The upper balloon is located in the right atrium–IVC junction, and the lower balloon in the infrahepatic IVC above the renal veins. Between these two balloons, a specialized fenestrated catheter isolates and collects the hepatic venous effluent; this is filtered in an extracorporal filtration system to eliminate melphalan. An additional lumen in the double-balloon catheter allows blood to bypass from the lower body. After the blood has been filtered, it returns to systemic circulation via an internal jugular vein sheath [34,35]. Before the procedure, patients received a chest X-ray, lung-function tests (capillary blood-gas analysis, spirometry, body plethysmograph, bronchial spasmolytic test, CO-diffusion capacity), doppler sonography of carotid arteries, and echocardiography and angiography, as clinically required [28]. Eligibility for PIHP was discussed by an interdisciplinary tumour board. Instead of performing regular treatment cycles every 4–8 weeks, we used a protracted treatment schedule in which we performed two cycles of PIHP at an interval of 4–10 weeks and then suspended treatment until further hepatic progression. A further two cycles of PIHP were then performed. Analysis included response rate; hepatic progression-free survival (hPFS) from first PIHP until both first progression and hepatic non-response to PIHP; and overall survival (OS) from first PIHP. Definite disease progression was determined by radiologic examination and the time at which lactate dehydrogenase (LDH), a serum marker for tumour burden, was not lowered by PIHP.

Case 1

A 37-year-old man who received a primary diagnosis of uveal melanoma in March 2014 returned to our department after diagnosis of hepatic metastasis confirmed by histology in June 2015. Because his serum LDH was normal, he received first-line immunotherapy with nivolumab 3 mg/kg bodyweight; this was discontinued after eight cycles in November 2015 because of disease progression and aggravation of his known spondyloarthropathy. He then received two PIHP cycles with melphalan within a 10-week interval. Tumour assessment showed response to treatment, and the patient continued nivolumab monotherapy for a further four cycles. Because his arthritis worsened, treatment was again discontinued. After four months without further treatment, new hepatic metastases were detected and a third PIHP was conducted in November 2016. At that time the patient had an increased serum LDH of 446 U/l. A fourth PIHP should have taken place six weeks later but was postponed to February 2017 (10 weeks later) because of an unspecific general infection. Post-treatment staging in March 2017 revealed growing and new hepatic metastases, and new lung and bone metastases. The patient died shortly afterwards, in April 2017. The first three PIHP cycles were generally well tolerated with grade-1 thrombocytopenia (Common Terminology Criteria (CTC)) and fatigue as the documented side effects. The fourth cycle induced more severe side effects, including pulmonary venous stasis with generalized oedema, tachycardia, hypoxaemia, fever, nausea, and fatigue with elevation of transaminases (alanine transaminase (ALT) CTC grade 1, aspartate transaminase (AST) CTC grade 2).

Case 2

A 65-year-old man who received a primary diagnosis of uveal melanoma in 2006 presented at our department in April 2013 with a single metastasis of the liver which was detected by CT and excised. In November 2013, new hepatic metastases were detected and immunotherapy with ipilimumab 3 mg/kg bodyweight was initiated . After four cycles, magnetic resonance imaging (MRI) confirmed hepatic progression. The first PIHP took place in May 2014 and the second PIHP eight weeks later in July 2014. First staging revealed regressive and stable metastases. The patient was monitored (PD-1 antibodies were not approved at that time) and a third PIHP was conducted seven months later when new hepatic progression was detected. At that time, the patient's serum LDH had increased to 594 U/l. The hepatic metastases responded to PIHP, LDH dropped to 344 U/l and the patient was monitored without further treatment. The patient remained stable for a further five months and then progressed again with disseminated hepatic metastases and a rapid decline in his general condition. The patient died in August 2015. As in case 1, the first two PIHP cycles were very well tolerated. Fever, vertigo, thrombocytopenia (CTC grade 1) and leukopenia (CTC grade 2) were reported after the third PIHP.

Case 3

A 53-year-old female patient who received a primary diagnosis of uveal melanoma in 2002 presented at our department in December 2011 after excision of hepatic metastases and detection of diffuse hepatic spread. Four cycles of immunotherapy with ipilimumab 3 mg/kg bodyweight were performed. Because of non-response, chemotherapy with gemcitabine and treosulfan was started in February 2013; this had no clinical benefit and led to a high tumour burden with an elevated LDH of 440 U/l. After the first PIHP in May 2013, the patient's LDH had already decreased to 254 U/l. As a result of coagulopathy, a high volume of blood was needed during intervention and weaning from general anaesthesia was prolonged. Leukopenia was the only side effect observed post intervention. A second PIHP was performed eight weeks later. Immunotherapy with a PD-1 antibody could not be given because its use had not been approved at that time. The patient was radiologically stable for seven months and received a third PIHP in January 2014. This cycle was not well tolerated, and the patient experienced severe arterial hypertension, coagulopathy, thrombocytopenia (CTC grade 2), leukopenia and anaemia (CTC grade 2), and pulmonic-venous stasis with generalized oedema. The patient also required assisted ventilation for three days. The uveal melanoma remained stable for a further 13 months of follow-up without further treatment. Six cycles of immunotherapy with pembrolizumab 2 mg/kg bodyweight were then given, with disease stabilization as best response. After further disease progression, a fourth PIHP cycle was conducted in April 2015 without further improvement. At that time, LDH was above 2000 U/l and the patient did not respond to treatment with sorafenib for three months, combination therapy with ipilimumab and nivolumab for four cycles, or to the use of the MEK inhibitor trametinib. The patient died in May 2016.

Case 4

A 79-year-old man who received a primary diagnosis of uveal melanoma in 2008 presented at our department in August 2018 after the detection of diffuse hepatic metastatic spread with histologic confirmation and suspicion of asymptomatic spinal metastases. The first PIHP took place in September 2018 and the second four weeks

later in October 2018. The patient's LDH decreased from 488 U/l to 281 U/l after the first PIHP and remained stable after the second PIHP. Both PIHP cycles were very well tolerated; laboratory results revealed transiently elevated liver enzymes (CTC grade 3). Six weeks later, staging revealed regressive liver metastases and new lung and progressive bone metastases. We then started an immunotherapy with pembrolizumab 2 mg/kg bodyweight in December 2018. After two cycles, the patient had to be treated in hospital due to newly diagnosed neuroborreliosis. After initiation of antibiotic treatment with ceftriaxone, pembrolizumab was continued. Staging in March 2019 revealed further regressive liver metastases, in addition to regressive lung and bone metastases.

Case 5

A 54-year-old female patient who received a primary diagnosis of uveal melanoma in February 2014 presented at our department in July 2016 after diagnosis of one liver metastasis and suspicion of a single spinal metastasis. After histologic confirmation and radiotherapy of the spinal metastasis, four cycles of an immunotherapy with pembrolizumab 2 mg/kg bodyweight were initiated, but the disease progressed with diffuse hepatic spread and further spinal metastases. Nine cycles of chemotherapy with gemcitabine and treosulfan were therefore started in December 2016, with stable disease as best response. As a result of further disease progression, particularly in the liver, the first PIHP took place in August 2017 and the second PIHP eight weeks later in October 2017. MRI revealed a partial response to treatment (Figure 1). The patient was stable for seven months thereafter without further treatment and then progressed, especially in the liver. A further two cycles of PIHP were performed in April 2018 and seven weeks later in June 2018. All PIHPs were well tolerated. No relevant side effects were reported apart from an already existing mild thrombocytopenia. An already increased LDH level before the third PIHP of 843 U/l decreased to 570 U/l eight weeks after the fourth PHIP. MRI after the fourth PIHP revealed regressive liver metastases, but progressive subcutaneous and bone lesions. A single bone lesion in the right femur was treated using radiotherapy because of imminent instability, and a therapy with ipilimumab 3 mg/kg plus nivolumab 1 mg/kg bodyweight was started in August 2018. Due to grade-3 autoimmune hepatitis, which required treatment with corticosteroids, immunotherapy was halted after three cycles. Subsequent staging revealed that the patient's liver metastases were still broadly stable, but also showed a progression of cutaneous, mammary, muscular, pancreatic, peritoneal and bone metastases. Therapy was changed to the off-label use of cobimetinib after informed consent. In additional, three vertebral metastases were treated using further radiotherapy because of possible instability. MRI eight months after the last PIHP showed further progressive disease with mainly stable hepatic metastases, but progressive abdominal, cutaneous and muscular metastases. Therapy was therefore changed to the multi-kinase inhibitor sorafenib.

Case 6

A 58-year-old female patient who received a primary diagnosis of uveal melanoma in December 2015 presented at our department in February 2018 with a first diagnosis of liver, lung and adrenal gland metastases confirmed by histology. Because the liver metastases were prominent, she received two cycles of PIHP at an interval of seven weeks in April and June 2018. Both PIHPs were well tolerated. Transiently elevated liver enzymes (CTC grade 1) returned to normal after the second PIHP. A mild leukopenia (CTC grade 1) occurred. The patient's LDH remained stable at a high level of 599 U/l before the first PIHP and 555 U/l after the second PIHP. MRI revealed stable disease

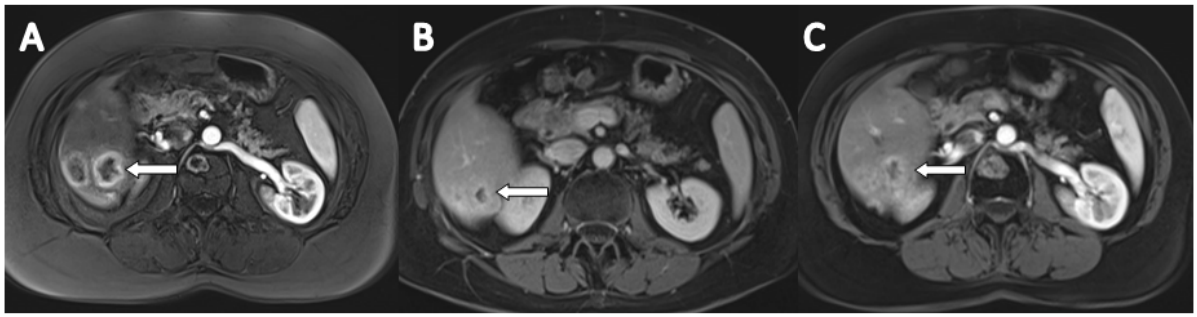

Figure 1: Contrast-enhanced MRI of the liver of patient 5 before (A), 2 months after (B) and 8 months after (C) the second PIHP.

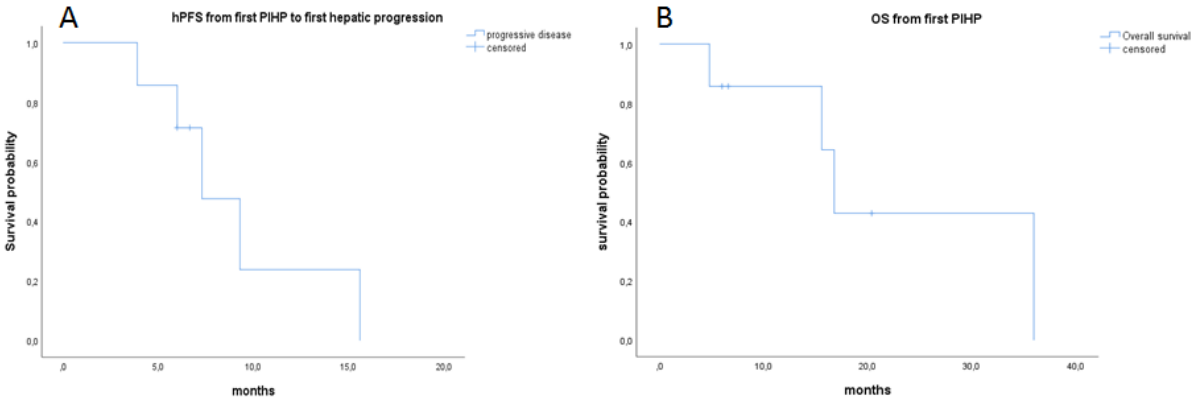

Figure 2: (A) PFS I (hPFS from first PIHP to first hepatic progression) (months), (B) OS from first PIHP (months).

for liver, lung and adrenal gland metastases, but also a new bone lesion. One cycle of immunotherapy with nivolumab 3 mg/kg bodyweight was given in July 2018. Because of severe abdominal pain, further cycles of immunotherapy had to be halted. Furthermore, a further MRI scan revealed a partial response of liver metastases, but also a single progressive lesion near the porta hepatis. Liver enzymes were slightly increased. The patient's general condition declined rapidly, and she died in September 2018.

Case 7

A 47-year-old female patient who received a primary diagnosis of uveal melanoma in May 2015 presented at our department in August 2018 with histologically confirmed liver metastases. She subsequently received two cycles of PIHP at a six-week interval in September and October 2018. Both cycles were tolerated without side effects. Staging until March 2019 showed stable liver metastases, but also growing bone metastases. It was therefore decided to add immunotherapy with a PD1 antibody and denosumab.

Results and Analysis of Patient Cases

Seven patients with hepatically metastasized uveal melanoma (three men, four women) with a median age of 51 years (range 37–68 years) were treated by means of repeated PIHP. Patient characteristics are presented in Table 1. All had extensive liver metastases, and increased

Patient	Sex	Age at first diagnosis of primary tumour (years)	Time until diagnosis of liver metastases (years)	Age at time of first PIHP	Best response to PIHP	Overall survival from first diagnosis of liver metastases (months)	Overall survival from first PIHP (months)	Treatment of liver metastases before first PIHP	Side effects of PIHP
1	m	37	1.2	38	SD	24	16.8	Metastasectomy, nivolumab (SD)	Thrombocytopenia, tachycardia, hypoxaemia, fever, nausea, fatigue, elevation of liver enzymes, pulmonary venous stasis with generalized oedema
2	m	58	6.7	65	PR	26.4	15.6	Metastasectomy, ipilimumab (PD)	Thrombocytopenia, leukopenia, vertigo, fever
3	f	44	9.4	53	SD	54	36	Metastasectomy, ipilimumab (PD), gemcitabine + treosulfan (PD), pembrolizumab (SD)	Coagulopathy, thrombocytopenia, leukopenia, anaemia, arterial hypertension, pulmonary venous stasis with generalized oedema
4	m	68	10.1	69	SD	8.4+	6.0+	None	Elevation of liver enzymes
5	f	51	2.5	55	SD	33.6+	20.4+	Pembrolizumab (PD), gemcitabine + treosulfan (PD)	Thrombocytopenia
6	f	58	2.1	58	SD	8.4	4.8	None	Leukopenia
7	f	45	1.3	47	SD	7.6+	6.6+	None	None

Table 1: Patient characteristics (m: Male. F: Female. SD: Stable Disease. Pr: Partial Response).

Patient	PIHPs conducted (cycles)	Time to next PIHP (weeks)	LDH (U/l) before PIHP (normal: <305 U/l)	Lowest LDH (U/l) within eight weeks after PIHP	LDH (U/l) at time of final radiologic hepatic progression	Progression I hPFS from first PIHP to first hepatic progression (months)	Progression II hPFS from first PIHP to final hepatic progression (months)
1	1	10	292	155	–	–	–
	2	36	155	202	–	9.3	–
	3	10	446	292	–	–	–
	4	–	1181	1390	1502	–	15.4
2	1	9	277	227	–	–	–
	2	30	266	166	–	6	–
	3	–	594	344	1538	–	14.3
3	1	8	440	227	–	–	–
	2	28	334	181	–	–	–
	3	65	270	239	–	15.6	–
	4	–	2039	533	698	–	24.9
4	1	4	488	281	–	–	–
	2	–	281	246	–	6.0+	6.0+
5	1	8	449	399	–	–	–
	2	26	455	523	–	7.3	–
	3	7	798	753	–	–	–
	4	–	753	570	–	7.3+	7.3+
6	1	7	599	337	–	–	–
	2	–	518	462	1655	3.9	3.9
7	1	5	149	204	–	–	–
	2	–	204	220	–	6.7+	6.7+

Table 2: Details of PIHPs conducted including LDH elevation and progression (hPFS: Hepatic Progression-Free Survival, + = Still On-going).

serum LDH (indicating a high tumour load) was observed before treatment in four of the seven patients (Table 2). Previous treatments received by four of the patients included surgical resection of hepatic metastases and immune-checkpoint blocker treatment including nivolumab and ipilimumab. The treatments received depended on when the drugs were approved and when the patient was treated. One of these patients had additional chemotherapy before planned PIHP.

Laboratory values taken before PIHP treatment showed elevated liver transaminases (AST/ALT) (CTC grade 1–2) in only one patient. Serum liver-function values, including quick testing, choline esterase and albumin, were within normal limits for all patients. Patients were treated with two cycles of PIHP at intervals of 4–10 weeks. First staging after these two cycles of PIHP revealed partial remission of metastases in one patient and stable disease in six. LDH as an indirect marker for tumour response decreased within eight weeks after PIHP for all four patients with elevated LDH before PIHP, resulting in LDH values within normal limits. Because PIHP has potentially severe side effects (e.g. patient case 3 at the third PIHP), further PIHP cycles were only administered when hepatic metastases progressed again. Between cycles, four of the seven patients received a PD-1 antibody, and one patient received combined immunotherapy with a CTLA4/PD-1 antibody as maintenance treatment. Median hepatic progression-free survival (hPFS, measured from first PIHP to first hepatic progression; progression I) was 7.3 months (range 3.9–15.6) (Figure 2). When progression of liver metastases was detected, the patients received their next two PIHP cycles. Serum LDH levels decreased again for all patients within eight weeks after the procedure, but all patients progressed shortly afterwards (Table 2). Median hPFS until final disease progression (measured from the first PIHP until progression despite PIHP, progression II) was 15.4 months (range 3.9–24.9). Overall survival after first diagnosis (stage IV) was 26.4 months (range 8.4–54.0), and overall survival after the first PIHP was 16.8 months (range 4.8–36.0). In general, most patients experienced only mild side effects, with nine CTC grade-1 AEs and four CTC grade-2 AEs. Three patients developed CTC grade-3 AEs, two of them after the first PIHP (coagulopathy, elevation of liver enzymes) and two after the third PIHP (coagulopathy, hypertension, pulmonary venous stasis with generalized oedema).

Discussion

PIHP is a minimally invasive treatment with generally acceptable toxicity for patients with non-resectable hepatic metastases. Higher chemotherapy doses can be used for PIHP than for systemic chemotherapies and other local hepatic treatments such as TACE (32, 35). In a phase-III study, 92 patients with hepatically metastasized melanoma received either PIHP or best alternative care (BAC). PIHP treatments were repeated every four weeks for a maximum of six cycles. A delay of four weeks per cycle was permitted to allow potential toxicities to resolve; if adverse events of grade 3 or 4 occurred, therapy was stopped. BAC in this trial consisted of systemic chemotherapy with or without chemoembolization, radioembolization or supportive care. hPFS was 7.0 months for patients who received PIHP and 1.6 months for patients who received BAC ($p < 0.001$). There was no statistically significant difference between OS for the PIHP group (9.8 months) and the BAC group (9.9 months). It is worth mentioning that the deaths of three patients were treatment-related: two died because of neutropenic sepsis and one because of hepatic failure. Approximately 75% of patients experienced grade 3 or 4 haematologic toxicity and 12% experienced significant hepatic toxicity [34]. In another study, PIHP treatment of patients with metastasized uveal melanoma at two institutions was analysed for safety and effectiveness. PIHP treatment was repeated approximately every eight weeks for up to six cycles and a median of two PIHPs was performed [35]. The number of treatments depended on the circumstances of individual patients and the local availability of resources. Adverse events were comparable to those in the phase-III study, in which hPFS was 9.1 months and median OS was 15.3 months. It was observed that high baseline LDH, high disease burden and the presence of extrahepatic disease at treatment onset were predictors for worse OS [36]. This seems to be in agreement with other studies in which low LDH levels were an independent baseline characteristic associated with favourable OS of patients with cutaneous melanoma [37-39]. In a retrospective analysis of seven centres performing PIHP in 18 patients with metastatic uveal melanoma, including patients from the Heidelberg centre, a median PFS of 12.4 months and median OS of 9.6 months from the first PIHP were observed. OS here was similar to OS in the phase-III trial. However, it remains unclear how PFS could be longer than OS, in view of the fact that both were measured from the first PIHP [22].

Because PIHP can be severely toxic, our uveal melanoma patients initially received only two cycles of PIHP at intervals of 4–10 weeks. Most patients tolerated these two cycles very well, with four patients developing mild adverse events (grade 1–2). Only two patients suffered grade-3 events. After careful discussion with the patient, we then monitored their clinical course without further treatment, or treated them with an anti-PD1 antibody ± ipilimumab until further disease progression was detected or until high-grade adverse events required treatment cessation. Using this treatment strategy, we achieved a median hPFS of 7.3 months (range: 3.9–15.6 months) and a median OS of 16.8 months (range: 4.8–36.0 months) from the first PIHP. Because we analysed data from seven patients only, conclusions should be drawn with caution; however, the length of overall survival observed here seems better than that previously reported for a disease with an expected median OS of less than one year. It appears that the hPFS achieved using this strategy is no worse than that of protocols with more than two PIHP cycles. Hence, two cycles of PIHP might sufficiently control the disease for several months, thereby protecting the patient from further toxicities. It is also possible that the PD-1 antibody received by five of the seven patients improved their clinical course. Retrospective analysis of uveal melanoma patients treated by use of immunotherapy has shown that the efficacy of this treatment is limited [40,41]. However, a reduction in tumour burden, as measured by a decrease in LDH after PIHP, might have increased the efficacy of subsequent immunotherapies. We achieved short-term responses by administering additional PIHP at disease progression, but response duration in this case was only short. Notably, further treatments after final progression to PIHP, including sorafenib, ipilimumab plus nivolumab or trametinib, also failed to stabilize the disease in any of the patients.

Limitations

These are the first reports on uveal melanoma patients receiving a protracted treatment schedule of only two initial courses of chemosaturation, followed by immunotherapy in some cases and liver retreatment at disease progression. Limitations of the study include its retrospective design, the heterogeneity of the treatments used and the small number of patients. However, because uveal melanoma is a rare disease, it is nonetheless important to share these first experiences. A randomized clinical trial should be performed to investigate the possible additional effect of the immunotherapy.

Conclusion

Although it is not possible to draw definitive conclusions from this small case series, the experiences described here suggest that two treatment cycles of PIHP might suffice to control hepatic metastasis of uveal melanoma for several months. Combination with a PD-1 antibody treatment might have helped to stabilize the disease after reduction of the tumour burden by PIHP. Side effects and treatment risks seem lower with this treatment scheme. Maintenance immunotherapy with an anti-PD1 antibody was administered safely and might be a good combination treatment with PIHP. Of course, a rigorous clinical study should be performed to investigate the possible role of immunotherapy in this situation.

Author Contributions

Lukas Trennheuser and Jessica Hassel had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Trennheuser: Conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, software visualization, writing.

Hassel: Conceptualization, methodology, project administration, supervision, writing, editing

Enk: Supervision.

Financial Disclosure

Lukas Trennheuser and Carsten Schulz: None reported

Jessica C. Hassel, MD (JCH) has had a paid consulting role with Merck and Pierre-Fabre, has received honoraria from Bristol-Myers Squibb, Merck, Novartis, Roche, Sanofi-Aventis and Pfizer and has received grant support from BMS.

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