A retrospective analysis of 141 patients with liver metastases from uveal melanoma: a two-cohort study comparing transarterial chemoembolization with CPT-11 charged microbeads and historical treatments

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We retrospectively evaluated the benefit of transarterial chemoembolization with CPT-11 charged microbeads (TACE) in 58 of 141 uveal melanoma patients with liver metastases. This was a retrospective analysis of a prospectively maintained database ranging from September 1990 to April 2014. Statistical analyses adjusting for possible confounding effects of extent of liver metastases were carried out using the Cox regression model under the verified hypothesis of proportional hazards. Among 141 patients with liver metastases, 58 were treated with TACE as first-line therapy and 36 were dead at the time of the analysis; 83 patients received other first-line treatments (deaths = 83). The treatment with TACE conferred a survival advantage (median 16.5 vs. 12.2 months, respectively); when the two cohorts were analyzed comparing the two groups according to the percentage of liver involvement, there was significant evidence that patients with worse hepatic involvement benefited most from the treatment (liver metastases = 20–50%: hazard ratio = 0.50, $P = 0.048$ and liver metastases ≥ 50%: hazard ratio = 0.17, $P = 0.009$). Liver function tests (transaminases and γ-glutamyl-transpeptidase) and age were higher in the historic group, and LDH tended to show higher values. There were no high-grade toxicities with TACE. TACE seems to be a tolerable regimen that confers an improvement in the survival of uveal melanoma patients with liver metastases. Confirmation of the clinical efficacy of TACE is recommended in a phase III trial, possibly with the inclusion of a targeted therapy such as a MEK inhibitor. *Melanoma Res* **25:164–168**

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Introduction

Uveal melanoma (UM) is the most frequent tumor of the eye in adult patients (70%), and represents 5–6% of all melanoma diagnoses. Its annual incidence is 0.7 : 100 000 for women and 0.5 : 100 000 for men, with a peak occurrence between 55 and 65 years of age. Approximately 40–60% of patients will ultimately develop metastatic disease. The prevalence of liver metastases is high; in fact, up to 95% of patients with metastases have liver involvement. Metastatic uveal melanoma (mUM) has a poor prognosis, with a median life expectancy of 2–5 months, and no standard therapy has been established so far [1].

Many systemic strategies based on immunotherapy (such as interferon and interleukin-2) or chemotherapy (including deticene, cisplatin, temozolomide, fotemustine, or thalidomide) have been studied for stage IV disease. Because of their limited efficacy and the high prevalence of hepatic involvement, several liver-directed approaches have been developed and proposed. Longest survivals are described for metastasectomy, with more than 29 months in a retrospective study on 16 patients [2], although patient selection bias was evident (patients had a limited metastasis burden and a long disease-free interval). In prospective case series of patients treated with pharmacological locoregional approaches, survival ranges from 5.0 to 24.0 months [3], but very limited phase III clinical trials are available. Although hepatic isolated perfusion (HIP) requires an open surgical procedure and cannot be repeated, several groups have developed different protocols within clinical trials [4–6]. The addition of TNF-α to melphalan in HIP for UM metastases has been reported in smaller case series. One trial on 22 patients found a significantly longer median duration of response for melphalan together with TNF-α (14 vs. 6 months); one toxic death occurred because of severe coagulopathy [6]. A phase III trial (NCT01785316) will

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evaluate whether HIP increases overall survival compared with the best alternative care (BAC); completion is expected in 2020. Percutaneous hepatic perfusion (PHP) was developed to avoid the open surgery necessary for HIP [7]. The update of a randomized phase III study that included 93 patients with liver metastases from cutaneous and ocular melanomas, treated with PHP versus BAC, reported a median survival of 9.8 months for patients treated with PHP, not different from the BAC arm; patients who crossed over from BAC to PHP arm had a median survival of 15.3 months. The most common grade 3/4 toxicities were thrombocytopenia and anemia, and three toxic deaths were registered after PHP [8]. Hepatic arterial infusion (HAI) with fotemustine ($N=30$) [9] and carboplatin ($N=8$) [10] conferred a median survival of 14 and 15 months; myelotoxicity was the most common adverse event in both studies. A recent randomized phase III trial compared intravenous versus HAI fotemustine and was interrupted at interim analysis for futility; the locoregional treatment was associated with a longer progression-free survival [hazard ratio (HR) = 0.62] and registered two toxic deaths in the HAI arm, but did not show an improvement in overall survival [11].

Transarterial hepatic chemoembolization with CPT-11-loaded drug-eluting beads (TACE)

Chemoembolization combines selective embolization and cytotoxicity of chemotherapy and shows clinical activity in several tumors, including UM [12], but no information exists for large cohorts. Agents used to perform chemoembolization include carmustine, carboplatin, cisplatin, deticene, fotemustine, granulocyte macrophage stimulating factor, mytomicin C, and CPT-11 [13–25]. The median overall survival ranged from 5 to 28.7 months; the procedure-related toxicities were usually not clinically significant, except for four septic deaths (21%) in the series described by Agarwala *et al.* [17] with cisplatin-based, thiotepa-based, and lipiodol-based procedures .

In the present report, 58 patients were treated with transarterial hepatic chemoembolization with CPT-11-loaded drug-eluting beads (TACE); of these, 49 received systemic fotemustine after the first TACE administration because of extrahepatic metastases or as consolidating treatment. The present study evaluates retrospectively the feasibility, tolerability, and effect on the survival of TACE in patients with liver metastases from UM, provides preliminary data on the safety of concomitant systemic fotemustine, and compares their outcomes with those of patients treated before the introduction of TACE.

Materials and methods

From September 1990 to April 2014 160 patients were treated for mUM at the Melanoma Oncology Unit of the Veneto Region Oncology Research Institute and were registered in a prospective observational study. Among these, 147 patients had liver metastases and 141 had sufficient data recorded to carry out the study and were analyzed under institutional review board approval.

The date of initial diagnosis, the date and site of metastases; date, type, and outcome of therapies; and the date of last follow-up or death and cause of death were collected from clinical records. Date and cause of death were collected by query of local registry offices and telephonic interview of the family or of the general practitioner for those patients lost to follow-up. We also recorded sex, age, performance status (PS), levels of LDH, ALP, γ-glutamyltranspeptidase (γGT), and transaminases both at diagnosis and after TACE. The localization and extension of metastases were measured by computed tomography at baseline and 4 weeks after treatment completion every 3 months during follow-up or the fotemustine maintenance phase. Liver metastases were recorded in our database as the percentage of liver replacement. We categorized the percentage of liver replacement into three groups: less than 20% of liver replacement, more than 20% but less than 50%, and more than 50%; the evaluation was carried out by the clinician and confirmed, by 3D reconstruction, with Syngo CT Oncology software (version 2009E; Siemens, Erlangen, Germany). Liver response was evaluated according to the RECIST 1.1 criteria (Response Evaluation Criteria In Solid Tumors) and also taking into account the percentage of necrotic tissue in the lesions after liver-directed treatments using mRECIST (modified RECIST). The choice of first-line therapy depended on the site of metastases and changed over time according to clinician decision and availability of clinical trials. The combination of interferon and tamoxifen was the most frequent scheme used in the first decade of the study, subsequently replaced by systemic fotemustine, with or without intra-arterial infusion, and, finally by TACE, which was introduced in our Institute in January 2009 (refer to Fiorentini *et al.* [22] for detailed procedure methods). Fotemustine was administered on an outpatient basis. TACE was performed in a day-hospital regimen; patients received a preparation for the procedure with morphine sulfate 10 mg and were usually discharged after an observation of 24 h, and antibiotic prophylaxis with ciprofloxacin 500 mg twice daily for 5 days was administered at home. From 2009, most patients diagnosed with liver metastasis have been treated with TACE irrespective of the presence of extrahepatic lesions. Only one patient was excluded because of hepatic artery thrombosis. PS, hematologic, hepatic, and/or renal function, patients' symptoms, life expectancy, and response to first-line treatments were determinants of further therapies. Associations between groups were analyzed by the χ^2-test or the Mann–Whitney U-test according to variables; survival was estimated using the Kaplan–Meier method and different cohorts were compared with log rank. The HR was estimated using a Cox multivariate regression model for proportional hazards. The Schoenfeld residual methodology was used to verify the proportional hazard assumption. A landmark analysis was

Table 1 Toxicities after the first transarterial chemoembolization

Toxicity	No pain	Mild	Moderate	Severe	Very severe	Requiring sedation	Not known
Abdominal pain	15	19	16	8	0	0	2
Toxicity (according to Common Terminology Criteria for Adverse Events v.4)	G0	G1	G2	G3	G4	G5	Not known
Nausea/vomiting	34	17	5	2	0	0	2
Thrombocytopenia	41	10	2	2	3	0	2
Neutropenia	30	25	2	0	1	0	0

additionally carried out to assess the survival according to response, with survival time defined from the first response evaluation 4 weeks after TACE. Patients whose death was unrelated to UM progression were censored at the last follow-up. Statistical analysis was carried out using R 2.15.2 (Linux version, survival and rms library, R Foundation for Statistical Computing, Vienna, Austria). All patients provided informed consent to the treatments and to the use of their clinical records for scientific purposes.

Patient characteristics

The cohort of 141 patients analyzed included 70 women (49.7%) and 71 men (50.3%). The median age at diagnosis of primary UM was 61.7 years (19.4–82.5) and that of first metastasis was 64.1 years (26.2–83.6) after a median disease-free interval of 24.0 months (0–254.3). At stage IV onset, most patients had the liver as the unique site of metastases ($N=101$, 71.6%); in 27 patients (19.1%), two organs were involved and in 13 patients (9.2%), three or more metastatic organs were involved. Most frequent associations were the liver and soft tissue (local relapse or distant dissemination, $N=22$, 15.6%), and liver and lung ($N=10$, 7.1%). Other sites of metastases were bone, adrenal, brain, gastrointestinal tract, and spleen. First-line treatment was administered within 4 weeks from the diagnosis of stage IV; 10 patients did not receive any treatment because of the patient's choice or poor PS.

Transarterial chemoembolization

A total of 58 patients (41.1% of 141) received TACE as the first-line treatment. Discharge was delayed after TACE for nine patients because of infection ($N=3$) and pain ($N=10$). Toxicities from TACE are shown in Table 1. The most frequent adverse event related to the procedure was pain (43 patients, any grade), which was mostly epigastric and treated with ranitidine (100 mg intravenously/day) for mild-moderate pain and with the addition of morphine sulfate (up to 40 mg intravenously/day) in eight patients with higher grade (G) pain. Nausea and vomiting were controlled with dopamine antagonists for patients with G1–2; the patients with G3 required ondansetron (up to 8 mg twice daily). The most serious adverse event was delayed protracted G4 thrombocytopenia, which required transfusion of platelets in two patients, and, in one patient, delayed G4 febrile neutropenia plus thrombocytopenia that required hospitalization to administer platelet transfusion and intravenous antibiotic and growth factor support. Two patients who developed fever more than 38.5°C with normal neutrophil count but elevated C-reactive protein received ceftriaxone (2 g/d intravenously) and recovered. No procedure-related deaths were observed. The day after TACE, we observed a median increase from baseline levels of LDH, AST, and ALT of 41 UI/l (range 15–9855), 15 UI/l (range 0–1133), and 17 UI/l (range 0–477), respectively, independent of response or toxicity. There was a trend inversely correlating the extent of liver involvement and disease response ($P=0.053$). TACE was repeated in patients who showed an incomplete response after first TACE or who experienced disease recurrence during follow-up up to six treatments (median three treatments/patient). In addition to TACE, 49 patients received intravenous fotemustine, the induction phase starting within 3 weeks from TACE. All G3 and G4 hematologic toxicities occurred in these patients.

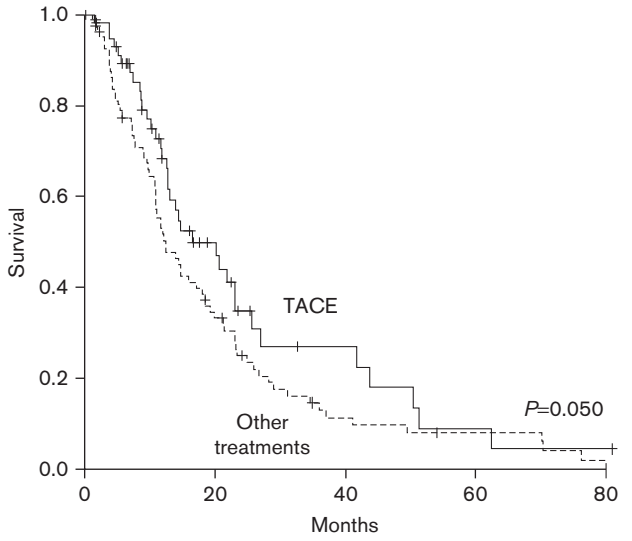
After a median follow-up of 11.4 months, 23 patients were alive or lost to follow-up; except for one patient who died from acute toxicity after HIP, all deaths were because of hepatic disease progression and failure. Our data showed that first-line treatment with TACE conferred a survival advantage compared with other regimens, with a median survival of 15.5 versus 11.5 months after the first treatment [6-, 12-, and 24-month survival were 89.0, 68.0, and 34.6% vs. 82.2, 58.9, and 28.7%, respectively ($P=0.050$)], as shown in Fig. 1. Cox regression analysis adjusting for baseline characteristics showed no survival benefit in patients with less than 20% liver replacement (HR = 0.95, 95% confidence interval (CI) 0.59–1.79, $P=0.88$), whereas survival was longer in patients with 20–50% (HR = 0.50, 95% CI 0.25–0.99, $P=0.048$) and with more than 50% liver replacement (HR = 0.17, 95% CI 0.04–0.64, $P=0.009$). The addition of systemic fotemustine only improved the outcome for patients with more than 50% liver replacement (HR = 0.25, 95% CI 0.07–0.99, $P=0.049$).

Univariate and multivariate analyses of survival were carried out. There was a trend toward lower age and baseline γGT in the TACE cohort (Table 2). Objective responses, evaluable according to the RECIST 1.1 criteria, were 42 (72.4%) stable disease (SD), 16 (27.5%) partial responses (PR), and 0 complete remissions (CR), with no influence on survival ($P=0.401$). According to mRECIST, we recorded two (6.9%) SD, 43 (74.1%) PR, and 11 (20.0%) CR, with a trend toward longer survival for patients with better response (median survival of SD, PR, and CR was 3.8, 20.2, and 23.0 months, respectively, $P=0.087$).

Discussion

mUM is a rare disease for which there is no standard or consistently effective treatment. Longer survival observed using liver-directed treatments, even in the presence of extrahepatic disease, suggests that liver disease control is crucial to improve the clinical outcome. In our experience, TACE seems to be, among the liver-directed treatments, the best tolerated and the only one that can be safely combined with systemic therapy with acceptable toxicity. The most common side effect was the postembolization syndrome, with abdominal pain, nausea, vomiting, elevation of liver enzymes, and fever. Previous TACE may have contributed toward high-grade myelosuppression, although this has been reported with a single agent fotemustine without TACE [11]. The observed benefit of TACE in our study requires confirmation in appropriately designed prospective clinical trials with stratification for prognostic factors. Retrospective cohort studies, such as ours, are subject to bias, notably through a long accrual period, patient selection, flexible protocol and schedule, imaging, and supportive care over time. However, all TACE procedures were performed by the same radiologist with a standardized procedure and imaging. We carried out statistical analyses to adjust for differences in patient characteristics and concluded that survival after TACE was longer than that in our historic controls.

Fig. 1



Overall survival. Treatment with transarterial chemoembolization (TACE) conferred a survival advantage.

The median survival and overall survival (15.5 months, 68.0 and 34.6% at 1 and 2 years, respectively), observed in the TACE-treated cohort, compare favorably with those published recently by Leyvraz *et al.* [11] with hepatic intra-arterial fotemustine (median survival 14.6 months and 2-year overall survival 19%), despite including patients with extrahepatic disease in our study. We used systemic fotemustine with TACE empirically because it is frequently used in mUM in Europe, is registered in Italy for use in metastatic melanoma, and several of our patients also had extrahepatic disease. However, the combination of a Topoisomerase I inhibitor, such as CPT-11, and alkylating agents may be synergistic, as shown in preclinical studies [26], suggesting that this approach could merit investigation in patients with large tumor burden or with extrahepatic metastases.

Considering the rarity of mUM, clinical trial accrual is difficult. Furthermore, patients with uveal and mucosal melanomas are often excluded from trials of novel agents in cutaneous melanoma. MEK inhibitors and new anti-angiogenic drugs are now under investigation [27] and combination therapy could improve results in mUM. In hepatocellular carcinoma, there is evidence that loco-regional hepatic treatment-induced devascularization is

Table 2 Prognostic factors in the treatment groups

	First-line TACE ($N=58$)		Other treatment ($N=83$)		Univariate	Multivariate
Variables	*N* (%)	Median (range)	*N* (%)	Median (range)	*P*	*P*
Sex					0.259	
Female	25 (43.1)		45 (54.2)			
Male	33 (56.9)		38 (45.8)			
Age at first metastasis (years)		61.8 (19.4–80.7)		65.0 (42.9–83.6)	**0.017**	0.087
DFI (months)		16.3 (0–154.0)		17.4 (0–254.0)	0.473	
PS					0.973	
0–1	51 (87.9)		77 (92.8)			
2–3	3 (5.2)		6 (7.2)			
Missing	4 (6.9)		1 (1.2)			
LDH (×UNL)		0.7 (0.6–0.9)		0.8 (0.6–1.5)	0.077	
γGT (×UNL)		0.5 (0.3–1.2)		1.9 (0.7–4.9)	**<0.001**	0.051
AST (×UNL)		0.5 (0.4–0.8)		0.9 (0.4–1.5)	**0.005**	0.360
ALT (×UNL)		0.5 (0.4–0.7)		0.9 (0.5–1.5)	**0.019**	0.151
Number of metastatic organs		1 (1–3)		1 (1–3)	0.597	

Bold values indicate the significance of *P* values.
DFI, disease-free interval; γGT, γ-glutamyltranspeptidase; PS, performance status (according to WHO categories); TACE, transarterial chemoembolization; UNL, upper normal limit.

transient and followed by upregulation of growth factors, which might contribute toward an accelerated progression at the periphery of the treated lesions [28–30]. The same type of tissue response could be evoked by TACE in mUM; hence, antiangiogenic drugs could be beneficial. We hope that our results prompt future studies in this disease with the aim of improving its dismal prognosis.

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Conflicts of interest

There are no conflicts of interest.

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