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Intra-arterial Hepatic Chemoembolization (TACE) of Liver Metastases from Ocular Melanoma with Slow-release Irinotecan-eluting Beads. Early Results of a Phase II Clinical Study

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Abstract. *Background: Uveal melanoma (UM) is the most common primary intraocular malignancy in adults and the liver is the predominant site of metastases (LM). If metastases appear, none of the systemic treatments established for cutaneous melanoma so far have any significant impact. Several authors have adopted trans-arterial chemoembolization (TACE) as palliation. TACE combines hepatic artery embolization with infusion of concentrated doses of chemotherapeutic drugs. DC Beads are new embolic products that can be loaded with irinotecan (IRI). The beads consist of polyvinyl alcohol microspheres modified with sulfonic acid groups and are available at different size ranges from 100 to 900 microns in diameter. The use of IRI as drug-eluting beads seems to optimize TACE in UM. Objective: Our purpose was to assess the safety and efficacy of this new kind of TACE in a phase II clinical study. Patients and Methods: Ten patients with LM from UM were treated with TACE-containing beads preloaded with IRI (100 mg). Results: All patients had an objective response, three presented a very good partial response and seven obtained a partial response. The median follow-up time from the beginning of therapy was 6.5 months (range 4-9 months). Eight patients are alive at the time of this analysis. The most important adverse event was abdominal pain during the procedure. Adequate supportive treatment with antibiotic and antiemetic prophylaxis, desametazone and intravenous hydration is strictly necessary until stabilization of serum levels of transaminases and to prevent infections. A major analgesic such as morphine must be used before and after the procedure. Conclusion: TACE containing beads preloaded with IRI is effective in the treatment of LM from UM. This approach seems to have better efficacy than previous TACE regimens adopted.*

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Uveal melanoma (UM) is a rare tumor but is the most frequent primary intraocular malignancy in adults (1) and represents about 6% of all melanoma diagnoses (2). The incidence of UM is reported to be 4,000 per year in the United States (2, 3). The 5-year overall survival for patients with ocular melanoma is estimated to be 50% to 70% (4). Factors related to the primary tumor that influence prognosis include cell type and number of mitoses, lesion size location, scleral or extrascleral invasion, extension beyond Bruch's membrane and optic nerve invasion (5). Approximately 50% of patients will develop metastases (6).

UMs have a significant tendency for metastasis to the liver (1). Up to 40% of patients have been reported to have hepatic metastases present at initial diagnosis and the liver becomes involved in up to 95% of individuals who develop metastatic disease (7). The liver is the predominant site of metastases in more than 80% of patients, with metastasis occurring *via* hematogenous spread (6, 8-11). Despite aggressive therapy, the median survival of patients after diagnosis of liver metastases is reported to be 2 to 7 months (12) and the 1-year survival is estimated to be 10% (13, 14).

Attempts have been made to define prognostic factors for patients with metastatic UM. A study of 201 patients with metastatic UM treated at one institution between 1968 and 1991 determined that only the metastasis-free interval and the serum alkaline phosphatase level were significant predictors of survival by multivariate analysis (13). In a multivariate analysis of 30 patients with disease confined to

the liver treated with hepatic intra-arterial administration of fotemustine, Leyvraz *et al*. (15) showed that the baseline lactate dehydrogenase (LDH) level was a strong prognostic factor for survival.

Metastatic UM has proven to be refractory to immunotherapy and chemotherapy regimens. Many systemic treatment strategies using immunotherapy, such as interferons and interleukin-2; chemotherapy, including dacarbazine (DTIC), cisplatin, temozolomide, or lomustine; or the antiangiogenic agent thalidomide, alone or in combination, have been used for patients with metastatic ocular melanoma (16, 17).

The use of DTIC and carmustine resulted in 4 partial responses (PR) in 25 patients treated with this regimen (18). The Southwest Oncology Group reported 1 complete response (CR) and 5 PRs in 64 patients treated with DTIC or cisplatin (19). Similarly, the M.D. Anderson Cancer Center reported a series of 129 patients who received chemotherapy, 99 of whom had not received prior systemic chemotherapy (13). Most of the drug regimens used DTIC, either alone or in combination with other agents. Only one patient treated with DTIC, 1,3-*bis*(2-chloroethyl)-1-nitrosourea (BCNU), vincristine and bleomycin had a PR. The Eastern Cooperative Oncology Group trials conducted by Albert *et al*. (20) in 1996 confirmed these results. Fifty-one patients with metastatic UM, 46 (90%) of whom had liver metastases (LM), were treated with various chemotherapeutic regimens, with no objective responses.

Pyrhonen *et al*. (21) also conducted a phase II trial with a bleomycin, vincristine, lomustine, DTIC and human leukocyte interferon regimen. Four out of 20 patients with metastatic UM achieved a PR. Similarly, Becker *et al*. (7) treated 48 patients with metastatic UM with subcutaneous interleukin-2, interferon 2-alpha, and fotemustine either intravenously or intra-arterially. They demonstrated an overall response rate of 14.5%; one patient achieved a complete response (CR), and an additional six patients experienced PRs.

Because of the limited efficacy of systemic regimens, the characteristic biology of metastatic spread confined to the liver and very limited survival associated with liver metastases, the investigation of measures to control hepatic disease progression seems justified. A number of locoregional treatment approaches directed to the liver are in clinical development for patients with ocular melanoma metastatic to the liver. Surgical approaches are not clearly indicated due to frequent liver relapses and distant spreading (22-24).

Several groups have reported their experiences with chemoembolization for patients with LM from UM (25-27). Hepatic artery chemoembolization (TACE) combines hepatic artery embolization with simultaneous infusion of concentrated doses of chemotherapeutic drugs (28). The theoretical advantages of this technique include rendering the tumor ischemic, achieving high drug concentrations within the tumor and reducing systemic toxicity. The tumor becomes ischemic because the afferent blood supply for macroscopic hepatic tumors is predominantly the hepatic artery (28-29). Irinotecan (IRI) has been reported to be active in a varierty of advanced recalcitrant solid tumor including melanoma (30). Tumor drug concentrations are reported to be 10 to 25 times higher than those achieved by infusion alone (31, 32) and the dwell time of the agents is markedly prolonged (33, 34). In addition, systemic toxicity is minimized because 85% of the drug is metabolized in the liver (35). Patients who may be considered candidates for TACE must have disease limited to the liver, a patent portal venous system, and no evidence of biliary obstruction.

Carrasco *et al*. (25) performed some of the preliminary work with this technique in their attempts to control ocular melanoma metastatic to the liver by using chemoembolization with polyvinyl sponge material and cisplatin. They reported regressions in two patients that lasted 19 and 6 months after one or two treatments. Similarly, Mavligit *et al*. (26) treated 30 patients with TACE by using an admixture of cisplatin and polyvinyl sponge. The overall response rate was 46%, with 1 CR and 13 PRs, and a median overall survival of 11 months. Treatment-related morbidity was limited and transient. Most recently, Agarwala *et al*. (27) conducted a phase I trial of TACE with cisplatin, thiotepa and lipiodol for primary and metastatic liver cancer, including three patients with ocular melanoma. Two of the three patients achieved PRs that lasted 3 and 16 months. Treatment-related mortality was not inconsequential: 4 out of 30 patients succumbed to gram-negative sepsis or cardiac events.

Patel SK *et al*. (28) adopted chemoembolization of the hepatic artery with BCNU in 24 patients. Eighteen patients experienced regression or stabilization of hepatic metastases. The overall response rate was 20.4%. They concluded that chemoembolization with BCNU is a useful palliative treatment for the control of hepatic metastases in UM patients.

Vogl T *et al*. treated 12 patients with liver metastases of UM with TACE and reported that the procedure was well tolerated in all patients without any relevant side-effects (29). Three patients responded to TACE, five patients with stable disease (SD), and four patients with progressive disease (PD). They concluded that repeated TACE offers a palliative treatment option in patients with oligonodular liver metastases from UM.

Based on these interesting data and on our previous experience (36, 37) using TACE with DC beads preloaded with IRI or doxorubicin in LM from colorectal cancer and primary liver tumours, we carried out a phase II study to assess the safety and efficacy of this new kind of TACE in LM from UM.

Table I. *Characteristics of the patients.*

Patients	Age (years)	Gender	Therapy of primary	Interval to liver metastasis (months)	% Substitution	Therapy of metastases	Interval from liver metastases to TACE (months)	No. of TACE	Response (RECIST)	Survival from TACE (months)	Site of relapse	ESAS Improvement	Status
1	54	M	E	36	75	IL2, INF, Cht	47	2	90%	4	None	No	D
2	62	M	RT	48	10	IA, IL2	84	2	70%	9+	Abdomen	Yes	A
3	45	F	E	0	60	IL2, Cht	24	1	60%	6	None	Yes	D
4	70	M	E	26	30	Cht, IL2	48	2	80%	9+	None	Yes	A
5	76	M	E	32	25	Cht	58	2	80%	8+	None	Yes	A
6	80	M	E	0	30	Cht	25	1	90%	6+	None	Yes	A
7	73	M	E	32	10	Cht	46	2	80%	5+	None	Yes	A
8	56	M	E	0	60	Cht IL2	26	1	70%	8+	Lungs	Yes	A
9	81	M	E	30	10	Cht	42	1	90%	3+	None	Yes	A
10	60	F	E RT	0	50	Cht IL2	28	1	70%	7+	None	No	A

E, Enucleation; RT, radiotherapy; IA, intra-arterial; IL2, interleukin 2; ChT, chemotherapy; IFN, interferon; D, dead; A, alive; M, male; F, female.

Patients and Methods

Between January 2007 and June 2008, ten patients presenting with LM from UM with a mean age of 65 years (range: 45-81 years) were enrolled in our study. All patients had previously been treated with enucleation (8 cases), radiotherapy (one case) or both (one case) for the primary tumour and systemic immunotherapy or chemotherapy for LM.

Patients presented normal liver function levels or up to 2x upper normal limit (UNL) at time of recruitment and had a performance status (Karnofsky) greater than or equal to 60%. The percentage of liver substitution was: up to 25% in 3 cases and up to 50% in 4 cases, up to 75% in 3 cases.

Clinical evaluation was performed before the procedure and one month after TACE by means of multi-detector-computed-tomography (MDTC). Follow-up assessments included verification of the clinical-laboratory status (marrow, liver and kidney function) and an MDTC (Brilliance 64 slice; Philips Medical Systems, the Netherlands). CT scans included triphasic study of the liver, with evaluation of the enhanced pattern of target lesions and tumor response rate according to modified RECIST criteria. Clinical complications were classified according to the WHO scale. Each patient was asked to fill in an ESAS (Edmonton Symptom Assessment System) questionnaire, a commonly used symptom assessment tool for advanced cancer and palliative patients to assess quality of life (38).

We adopted the same program of supportive treatment and intra-arterial lidocaine used in a previous study (36). The prophylactic treatment to prevent renal failure was *i.v.* hydration which started on the day before TACE and continued on days 0-2 with 2,000 ml (1,000 ml of saline solution, 1,000 ml of 5% glucose) with the addition of 900 mg ranitidine, infused for 24 hours. Ranitidine was used to reduce the risk of gastric and pancreatic toxicity. The prophylactic treatment against nausea and vomiting was based on 5 mg tropisetron, 1 vial before TACE and 1 vial after 6 hours on day 0; and 8 mg dexamethasone at 08.00 am and 08.00 pm on days 0-5. The prophylactic treatment against pain was based on 10 mg morphine, 1 vial 30 minutes before and 6 hours after TACE. Intra-arterial lidocaine (5 ml) was infused selectively to the vascular bed to be treated immediately before TACE. Prophylactic treatment against infection was based on 2,000 mg cefazolin at 08.00 am and 08.00 pm on days 0-2. The supportive treatment was maintained whenever required on days 3-5.

Drug preparation. The saline suspension in the DC Beads microspheres (DEB; Biocompatibles UK, Surrey, UK) was removed and the beads were mixed with an IRI solution at a dose of 100 mg per 2 ml at least two hours before the procedure.

Digital subtraction angiography (DSA) was performed transfemorally. The study performed was extended to the abdominal aorta to assess hepatic circulation and blood supply to the tumour, with subsequent therapeutic planning. Following insertion of a 5-F Cobra or Simmons catheter, a 3-F microcatheter (Renegade Hi-Flo; Boston Scentific, MEDI-TECH, USA) was then placed and selective hepatic catheterisation of lobar or segmental branches afferent to the neoformed tissue was performed in all patients.

DC Bead infusion was preceded by selective intra-arterial infusion of 5 ml of 1% lidocaine to reduce the local pain, and verapamil for arterial vasodilation and to prevent vasospam induced by contact of the drug with the endothelium of the vessel.

Subsequently, for every TACE, 100-200 mg IRI preloaded in 2-4 ml beads of 100-300/300-500 μm were administered.

A total of 15 TACE procedures were performed. In five cases, only one cycle of TACE was administered; in five cases, 2 cycles. We obtained 100% technical success in 15 of the TACEs performed and no complications due to the procedure occurred.

Study endpoints. The primary objective of this study was to determine the safety, feasibility and tolerance of TACE adopting irinotecan-loaded microspheres. The secondary objective was to evaluate the response rate, quality of life and survival.

Results

Ten patients, 8 males and 2 females, aged 65 (45-81) years with UM metastatic to the liver were treated (Table I).

The primary UM was enucleated in 8 cases, treated with radiotherapy in one case, and with both modalities in one

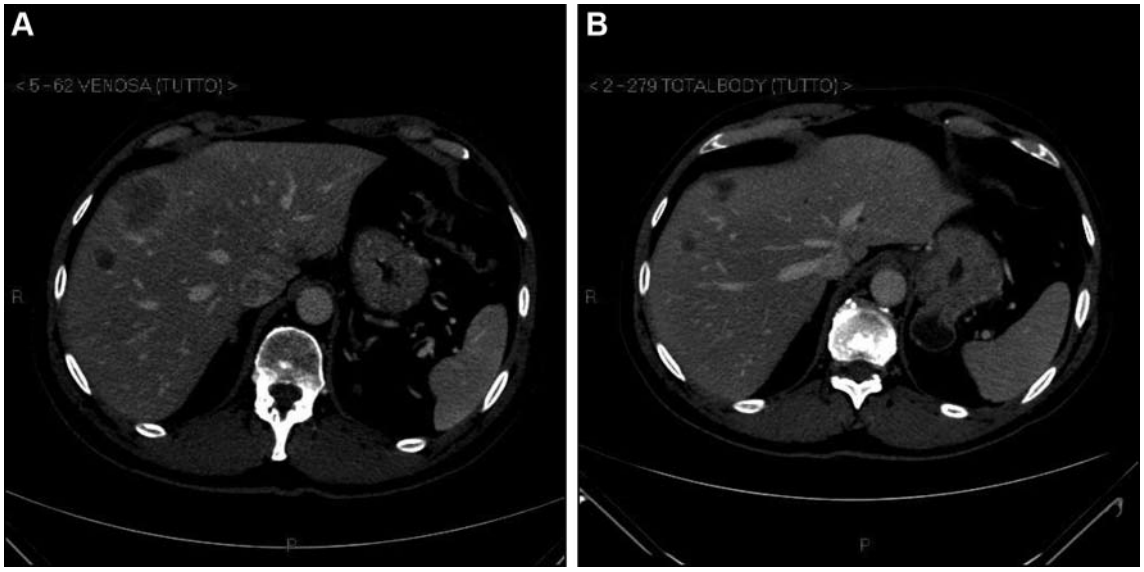

Figure 1. *Magnetic resonance image of (MRI) of multiple liver metastases from uveal melanoma. A, MRI before TACE; B, MRI 3 months after TACE.*

case. The LM were metachronous in seven cases and in three were synchr to the diagnosis of UM. The median metastatic interval from the treatment of primary UM to the onset of LM was 34 (10-75) months. All patients received chemotherapy and immunotherapy for LM; one received intra-arterial perfusion with fotemustine. Ten patients obtained an objective response to TACE.

Following RECIST criteria, 3 patients had a major response with evidence of metastases reduction of 90% , 3 patients had a reduction of 80% and 4 patients presented a reduction between 70% and 60% . Treatment-related morbidity was short-lived and included grade 2 primarily upper right quadrant abdominal pain after 12 TACE and grade 3 after 3 TACE; 1 transient paralytic ileus lasting 4 days, and 2 cases of nonicteric hepatitis. No hematological toxicity or alopecia was reported. The median duration of hospitalization was 3 days (range 1-5). The percentage of liver involvement was linked to response: 3 patients with oligonodular metastases, up to 25% of substitution, obtained the best reduction of metastases, close to complete (Figure 1). Three patients with multiple nodular substitution up to 75% had less evidence of response.

The median follow-up time from start of therapy was 6.5 (range 4-9) months. Eight patients are alive at the time of writing. Two patients with 75% and 60% of liver substitution, died after 4 and 6 months respectively due to rapid progression in the liver.

All the patients were requested to fill in an ESAS questionnaire to assess their quality of life. Eight patients reported a personal improvement (80%). Dose-limiting toxicities for IRI, such as diarthea or of the bone marrow, were not reported by any patient.

Discussion

Ocular melanomas can arise from the choroid, ciliary body or iris, and are completely different from their cutaneous or mucous membrane counterparts in terms of molecular pathogenesis, histology, natural history and response to therapy. The liver is the most prevalent site of metastases in UM and in more than 50% of cases metastases are limited to the liver (9-11). The prognosis of untreated patients with LM is poor and none of the systemic treatments established for cutaneous melanoma have so far had any significant impact. On the other hand, our study, as well as reports by others (Table II) demonstrate the efficacy of TACE in patients suffering from this condition. Moreover, we report a higher number of PRs.

Mavglit *et al*. treated 30 patients with ocular melanoma metastatic to the liver by hepatic arterial chemoembolization using an admixture of cisplatin and polyvinyl sponge (PVS) (26). Tumor regression was complete in one patient and partial (greater than 50%) in 13 patients. The total response rate was 46% . The median survival for the entire group was 11 months (95% confidence interval, 9 to 18 months). Treatment-related morbidity was short-lived and included primarily severe upper right quadrant abdominal pain, transient paralytic ileus, and nonicteric hepatitis. They concluded that hepatic arterial chemoembolization provided effective palliation, with good-quality survival among 46% of patients with ocular melanoma metastatic to the liver. The response rate is lower than our results probably due to the size and irregular shape of PVS. This does not allow an efficacious distal occlusion of intratumoral vessels.

Table II. *Results of TACE in liver metastases from primary uveal melanoma.*

Author	Type of TACE	Number of patients	Overall response rate (%)	Median survival (months)
Mavligit *et al*. (26)	Cisplatin+polyvinyl sponge	30	46	11
Agarwala *et al*. (27)	Cisplatin+polyvinyl sponge	19	16	8.5
Patel *et al*. (28)	BCNU+etiozide oil+gelatine sponge	30	17	5
Vogl *et al*. (29)	MMC+lipiodol+resorbable microsphere	12	25	21
Present report	Slow-release irinotecan-eluting beads	10	100	NR

BCNU, 1,3-*bis*(2-chloroethyl)-1-nitrosourea; MMC, mitomycin C; NR, not reached at 7 months.

Agarwala SS *et al*. conducted a randomized phase I/II trial evaluating escalating doses of intrahepatic chemotherapy with cisplatin with or without PVS in 19 patients with ocular melanoma and liver metastases (27). The cisplatin dose was initiated at 100 mg/m^2 and was increased in 25% increments. Patients were randomized to receive cisplatin alone or cisplatin plus PVS. Seven patients were treated with intrahepatic cisplatin at 100 mg/m^2: four with PVS, and three without. The dose was escalated to 125 mg/m^2 with or without PVS in the remaining 12 patients. The maximum tolerated dose for intra-hepatic cisplatin was determined to be 125 mg/m^2 with or without PVS. The overall response rate was 16%. Dose-limiting toxicities included renal, hepatic and hematological effects. They concluded that this therapy produced an interesting response rate in patients with LM from UM. The toxicities are higher than those reported in our study and confirm the limitations in the use of PVS with respect to more modern embolizing agents.

Patel *et al*. conducted a phase II clinical trial for patients with LM from UM using chemoembolization of the hepatic artery with BCNU dissolved in ethiodized oil (28). Gelatin sponge particles were used as a transiently occlusive agent. Twenty-four patients out of thirty completed at least one treatment to all targeted liver metastases and were evaluable for hepatic response. Eighteen of these twenty-four patients experienced regression or stabilization of hepatic metastases for at least 6 weeks (one CR in hepatic metastases; four PRs; 13 SDs). One of the thirteen patients with SD was rendered free of disease by surgical removal of metastases after chemoembolization (surgical CR). The overall response rates (complete and partial responses) for intention-to-treat patients and for patients who were evaluable for response were 16.7 and 20.4%, respectively. The median overall survival of the entire intention-to-treat group of patients was 5.2 months (range, 0.1-27.6 months); for patients with complete or partial response in hepatic metastases 21.9 months (range, 7.4-27.6 months); for patients with stable disease 8.7 months (range, 2.9-14.4 months); and for patients with progressive disease 3.3 months (range, 1.6-5.6 months). This paper reports a 20% of responses and shows the possibility of benefits from a further surgical approach. On the contrary, there was no surgical removal of metastases because of the small number of our patients. We will continue to pursue this neo-adjuvant approach. Thirteen out of the eighteen patients who achieved CR, PR or SD, subsequently developed progression of extrahepatic metastases with control of hepatic metastases. The authors concluded that chemoembolization with BCNU is a useful palliative treatment for the control of hepatic metastases in patients with UM. However, progression in extrahepatic sites after stabilization of hepatic metastases requires further improvement in the therapeutic approach to this disease.

Vogl *et al*. treated 12 patients with liver metastases of UM with TACE (29). Six patients presented with solitary liver metastases (6-12 cm in size) and six patients with oligonodular metastases (n≤6). The embolization suspension consisted of a maximum of 10 mg/m^2 mitomycin C, 10 ml lipiodol, and an injection of 200-450 mg resorbable microspheres for vascular occlusion. In the follow-up, magnetic resonance imaging was performed at 3-month intervals. They reported that the TACE procedure was well tolerated in all patients without any relevant side-effects. Three patients responded to TACE with a size reduction of more than 50% (PR), five patients with stable disease, and four patients with progressive disease with an increase in volume of more than 25%. Mean survival following primary tumor treatment was 32.9 months, and after first embolization 19.5 months. Lower survival rates were recorded for the progressive group (16.5 months). They concluded that repeated TACE offers a palliative treatment option in patients with oligonodular liver metastases of uveal malignant melanoma. The TACE proposed has been performed with mitomycin that is not efficacious in UM. Furthermore, the mixture of lipiodol and resorbable microspheres seems to induce a short-lasting vascular occlusion. In this study, the rationale, the pharmacokinetic properties and the actual drug uptake advantage of resorbable microspheres are not clearly reported.

Comparing our data with all the previous reports, our study introduces a new TACE with beads, presenting more

detailed and widely studied pharmacological aspects (36, 37, 39, 40) and quality of life assessments show a significant improvement in 8 out of 10 patients.

Conclusion

One of the limits of TACE was the difficult repeatability and the standardization of the method. Even if many authors have reported clinical advantages, it is clear that the approach is empiric and personal without the possibility to draw conclusive data. Our study demonstrates that it is possible to define methods of treatment and support well. We hope that other authors will confirm this.

Our data show that TACE adopting the new embolic material DC-Beads preloaded with IRI is highly effective in LM from UM. Intensive support therapy to reduce side-effects is necessary. Prolonged follow-up is still being carried out to better define the therapeutical results of this approach. Symptom assessment scales such as the ESAS work well to make symptoms manifest. Listing symptoms on a problem list is a necessary step in addressing and reducing them in UM patients receiving TACE (38).

In oligonodular UM it should be possible to offer to the patients a surgical removal after a succesful TACE.

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