Adjuvant intra-arterial hepatic fotemustine for high-risk uveal melanoma patients

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Uveal melanoma metastases occur most commonly in the liver. Given the 50% mortality rate in patients at high risk of developing liver metastases, we tested an adjuvant intra-arterial hepatic (i.a.h.) chemotherapy with fotemustine after proton beam irradiation of the primary tumour. We treated 22 high-risk patients with adjuvant i.a.h. fotemustine. Planned treatment duration was 6 months, starting with four weekly doses of 100 mg/m^2, and after a 5-week rest, repeated every 3 weeks. The survival of this patient group was compared with that of a 3 : 1 matched control group randomly selected from our institutional database. Half of the patients experienced $\geq$ grade 3 hepatotoxicity (one patient developing cholangitis 8 years later). Catheter-related complications occurred in 18%. With a median follow-up of 4.6 years for the fotemustine group and 8.5 years for the control group, median overall survival was 9 years [95% confidence interval (CI) 2.2–12.7] and 7.4 years (95% CI 5.4–12.7; $P = 0.5$), respectively, with 5-year survival rates of 75 and 56%. Treatment with adjuvant i.a.h. fotemustine is feasible. However, toxicities are important. Although our data suggest a survival benefit, it was not statistically significant. Confirming such a benefit would require a large, internationally coordinated, prospective randomized trial. ***Melanoma Res*** **18:220–224**

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Introduction

Melanoma of the eye is a rare disease with an incidence estimated at 0.6 per 100 000 persons/year. However, it is the most common intraocular tumour [1–3]. While sharing a common embryonic origin with its cutaneous counterpart, uveal melanoma is characterized by an inherently unique clinical and biological behaviour. The eye lacks the lymphatic vessels found in the skin, and metastatic spread of uveal melanoma is thus mainly haematogenous with initial metastatic spread to the liver in over 90% [4]. This 'oculohepatic' tropism accounts for the poor overall outcome of patients with uveal melanoma with mortality rates at 5 years ranging from 20% for small tumours to 50% for large tumours [5].

Several prognostic factors have been recognized as associated with an increased risk of developing liver metastases: tumour diameter [especially a largest tumour diameter (LTD) >20 mm] and height, location of the tumour anterior to the equator of the eye and extrascleral extension of the tumour into the vortex veins. Histopathological characteristics, such as epitheloid cell rather than spindle cell type, and cytogenetic alterations, such as monosomy 3, have also been shown to be associated with reduced overall survival [6–8].

Few therapeutic options exist once liver metastases are established. In historical series, median survival from diagnosis ranges from 2 to 6 months, with only 15% of patients surviving more than 1 year [9–11]. Systemic chemotherapy is largely ineffective, with reported response rates inferior to 10% [12–14]. Locoregional approaches have been more promising. In particular, measurable antitumour activity has been demonstrated with direct administration into the main hepatic artery of fotemustine, a third-generation chlorethylating nitrosurea. We recently reported data confirming the results of our initial phase II study of intra-arterial hepatic (i.a.h.) fotemustine in patients with liver metastases from uveal melanoma [15]. In over 100 patients the overall response rate was 36%, with 1-year and 2-year survival rates of 67 and 29%, respectively [16].

Given the promising activity of i.a.h. fotemustine in metastatic patients and preclinical evidence that adjuvant therapy might reduce the occurrence of liver metastases

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[17,18], we developed a strategy of adjuvant i.a.h. fotemustine for patients at high risk of liver relapse.

Patients and methods

Patients

Between 1997 and 2005, we treated 22 patients presenting with nonmetastatic uveal melanoma. To be eligible for treatment with adjuvant i.a.h. fotemustine, patients had to meet at least one of the following inclusion criteria: choroidal involvement, LTD >20 mm, extrascleral extension and tumour height >15 mm. Sixty-six matched controls for the main patient and tumour characteristics (Table 1) were selected from our institutional database of 2993 patients. All 88 patients underwent proton beam irradiation of the primary tumour. All patients gave their oral consent. Data analysis was done after chart quality assessment with authorization by the local Ethics Committee.

Treatment

Adjuvant treatment started 4–6 weeks after the end of proton beam irradiation of the primary tumour. Fotemustine (Muphoran) was supplied by Servier Inc. (Paris, France), as a freeze-dried sterile powder in vials containing 200 mg of active substance. For i.a.h. infusion, the drug was dissolved with 4 ml of ethanol, then further diluted in 250 ml of 5% injectable glucose solution and protected from light. An implantable catheter connected to a subcutaneous access chamber (Port-A-Cath) was surgically placed into the hepatic artery through the gastroduodenal artery or radiologically according to the technique described by Herrmann *et al.* [19]. Fotemustine (100 mg/m^2) was then administered intra-arterially as a 4-h infusion. A 4-week induction period (with weekly administrations on days 1, 8, 15, 22) was followed by a 5-week pause and then by maintenance treatment every 3 weeks for an overall treatment duration of 6 months. Patients received prophylactic antiemetic treatment using ondansentron and methylprednisolone. Toxicity was graded according to the International Common Toxicity Criteria (NCI, NIH, version 2.0, March 1998).

Follow-up

Follow-up visits were performed twice a year and included a physical examination, liver function and haematological blood work, and liver imaging by ultrasonography, computed tomography scan or MRI.

Statistics

A control group of 66 patients was randomly generated from the hospital registry of all uveal melanoma patients treated in Lausanne. Three matched controls were selected for each patient treated with adjuvant fotemustine. All controls were selected from 1686 patients undergoing the same initial therapy as the experimental group, namely proton beam irradiation of the primary tumour, within the same period (after 1994). They were matched according to the most important prognostic factors: extrascleral extension (present vs. absent), LTD (10–15 vs. >15–20 vs. >20 mm) and age at primary treatment (≤ 55 vs. >55 years). An imbalance in the age distribution between the fotemustine and the control group (Table 1) is explained by the fact that matching for age was not possible for patients in two among the seven combinations of these factors in the fotemustine group (the number of available controls after matching for extrascleral extension and tumour diameter being insufficient to permit further stratification for age).

Overall survival was defined as time from the start of proton beam irradiation to death. The survival status of all 88 patients was updated during late 2006/early 2007. Patients still alive at that time were censored at the date of last contact. Seven patients in the control group had been lost to follow-up at the time of analysis. Percentages of events of interest over time were calculated by the Kaplan–Meier method and corresponding standard errors with Greenwood's formula [20]. For survival comparison, the *P* values were calculated using the log-rank test. A Cox regression model was applied, with extrascleral extension and LTD identifying strata and the other factors entered as covariates [age, gender, tumour thickness (<3 vs. 3.1–5 vs. 5.1–10 vs. >10 mm), ciliary body involvement (yes vs. no)], appropriately coded into binary variables. Comparison of patient characteristics between fotemustine patients and controls was performed with Fisher's exact test. All probability values were for two-sided tests. Analyses were performed with the statistical package SPSS (Chicago, Illinois).

Table 1 Matching groups

				Controls, *N*			
Extrascleral extension	Largest tumour diameter, mm	Age, years	Fotemustine, *N*	Needed for three controls/case	Available	Selected	Matching category
Absent	>20	20–55	11	33	101	33	A
		>55	1	3	142	3	B
Present	10.1–15	>55	1	3	9	3	C
	15.1–20		1	3	24	3	D
	>20	20–55	6	18	7	6	E
		>55	2	6	19	18	F

Results

Between 1997 and 2005, 22 patients presenting with high-risk uveal melanoma were treated with adjuvant i.a.h. fotemustine. Patient characteristics were as follows: six women and 16 men, with 17 patients in the age group 20–55 years and five patients older than 55 years. In the control group, there were 39 men and 27 women, and 39 patients were in the age group 20–55 years and 27 patients were older than 55 years. The characteristics of the fotemustine and the control group were well balanced with regard to extrascleral extension and LTD with the exception of the age distribution within the LTD and extrascleral extension group (groups E and F in Table 1). This imbalance, however, owing to an insufficient number of available controls, did not affect the overall analysis given that LTD and extrascleral extension are the most powerful predictors for liver metastases.

A total of 167 infusions of fotemustine were administered, with a median of nine administrations per patient (range 3–10). Five patients (23%) received only the induction cycle (three to four infusions), with early treatment cessation owing to hepatic toxicity ($n = 4$) and/or catheter-related complications ($n = 2$). Overall, complications of the intra-arterial catheter such as dislocation or thrombosis occurred in four patients (18%) and led to treatment discontinuation after 3–8 administrations of i.a.h. fotemustine (Table 2).

The main side effect of the adjuvant treatment was drug-induced hepatitis: grade 3–4 transaminase elevation was observed in 10 patients (45%), grade 3–4 gamma glutamyltransferase/alkaline phosphatase elevation in 11 patients (50%) and grade 3–4 elevated bilirubin levels in three patients (14%). In four of these patients (18%) treatment had to be stopped after the induction cycle. Liver function tests recovered to baseline levels in all patients after the end of therapy. One patient developed necrotic cholangitis 8 years after chemotherapy (Table 2) without disease recurrence.

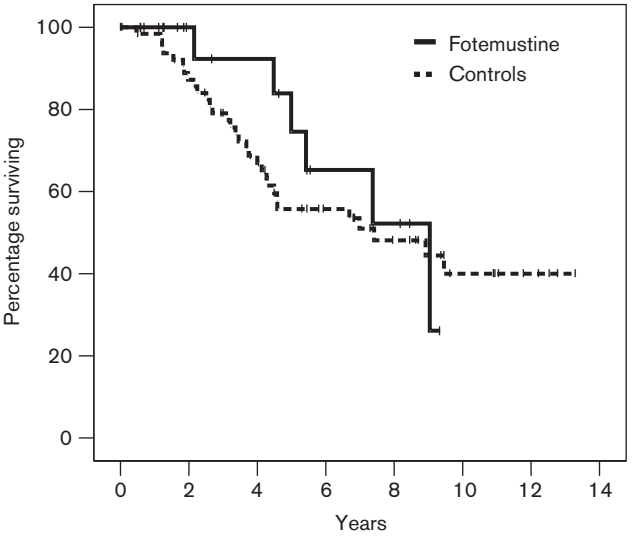
Three patients experienced grade 3 gastric toxicity: gastritis in one patient, epigastric pain in another and gastric ulcer with grade 2 anaemia in a third. As expected, given the high hepatic extraction rate, haematotoxicity was generally not an important concern with i.a.h. fotemustine. Two patients presented with grade 3 neutropenia and one patient with grade 3 thrombocytopenia.

Table 2 Toxicity grades 3 and 4

Toxicity	*n*	(%)
Transaminases	10	45
γGT/AP	11	50
Bilirubine	3	14
Gastric	3	14
Neutropenia	2	9
Thrombocytopenia	1	5
Catheter related	4	18
Necrotic cholangitis[a]	1	5

AP, alkaline phosphatase; γGT, gamma glutamyltransferase.
[a]Eight years after treatment.

Fig. 1



Overall survival.

Median follow-up was 4.6 years for the experimental group and 8.5 years for the control group. Median survival for patients treated with fotemustine was 9 years (95% confidence interval (CI) 2.2–12.7) compared with 7.4 years in the control group (95% CI 5.4–12.7). The corresponding 5-year survival rates were 75 and 56%, respectively ($P = 0.539$) (Fig. 1). The estimated hazard ratio for death at 5 years was estimated at 0.98, with a 95% CI of 0.38–2.61, $P = 0.981$ (see the statistical section for details of the analysis model used).

Four of the seven patients who developed liver metastases in the fotemustine group had experienced a previous local relapse, occurring 4 months to 2.5 years before distant relapse. However, local relapse in these patients occurred late, from 3.5 –7 years after the end of adjuvant chemotherapy. These findings are only observational, disease recurrence not formally being assessed within the control group.

Discussion

Uveal melanoma is an uncommon disease characterized by a particular 'oculohepatic' tropism that accounts for a high incidence of liver metastasis and high mortality rates. In consequence, efforts are currently ongoing to further understand its particular biology and clinical behaviour and to improve therapeutic strategies. Liver metastases are generally diagnosed within 2 years of

diagnosis of the primary tumour, but can occur as late as 30 years after primary treatment [16,21].

As the liver is the first, and often the sole metastatic site, many investigators suppose the liver to be a sanctuary for circulating tumour cells. Only a few reports exist on adjuvant chemotherapy in uveal melanoma patients. The largest randomized trial available, the results of which have been recently updated, compared adjuvant intravenous dacarbazine with observation [22]. Adjuvant chemotherapy with dacarbazine was not associated with prolonged survival or reduced incidence of distant metastases, although the negative results of this study might be explained by a selection of patients with a relatively low-risk profile.

We developed a strategy of adjuvant i.a.h. fotemustine to investigate whether the locoregional administration of chemotherapy early in the disease course might eradicate occult micrometastases, and thus prevent disease recurrence in the liver in high-risk patients. Only patients with an estimated risk of death of $\geq 50\%$ at 5 years were eligible for this procedure [5]. As all patients were diagnosed by clinical means and treated conservatively with proton beam radiotherapy, we used as selection criteria clinical – and not histopathological or cyto-Genetic – tumour characteristics, that is, the presence of an extrascleral extension and/or a large tumour size with a diameter > 20 mm.

We performed a comparison with a matched series to approximately assess the relative effect of adjuvant treatment with fotemustine. The primary aim was to evaluate whether the strategy should be further investigated within a prospective randomized trial.

Although the log-rank comparison of the survival curves did not show a statistically significant difference, a small survival benefit might exist during the first 2–5 years, reflected by a trend towards improved survival from 56 to 75% at 5 years. To estimate the influence of fotemustine on patients' survival within the present analysis, it is important to stress that the control group is a representative cohort of high-risk patients. A mortality rate of almost 50% is in line with what has been known for decades for high-risk patients treated with enucleation [5]. It is noteworthy that all 88 patients in the present series were treated with proton beam irradiation despite relatively locally advanced tumour stages. It is now widely recognized that proton therapy is equivalent to enucleation in terms of local control and overall survival [23]. Recently, we have reported that proton therapy can sterilize almost any tumour volume, and therefore enucleation can be avoided in a large number of patients [24]. Therefore, the possibility that the control group had a particularly favourable profile limiting a potential effect of fotemustine can be ruled out.

The pattern of recurrence in the fotemustine group is characterized by a relatively high local (intraocular) recurrence rate of 23% (5 patients), compared with the overall local recurrence rate of 1.1% achieved in uveal melanoma patients treated with proton beam radiotherapy in Lausanne and Villigen since 1994 [25]. However, these relapses occurred late after adjuvant chemotherapy with disease-free intervals ranging from 3.5 to 7 years. Four of the seven patients who developed liver metastases had previously experienced local recurrence. Although this is only a single observation finding, it is possible that in high-risk patients living long enough after adjuvant i.a.h. fotemustine to experience local relapse, the local relapse may subsequently give rise to haematogenous tumour cell spread to the liver. Thus, adjuvant chemotherapy in such patients might eradicate occult metastases from the initial tumour, but not prevent subsequent metastases from a recurrent local tumour. Unfortunately, there are no comparative data available on disease recurrence in the control group.

The potential benefit of adjuvant i.a.h. fotemustine might have been additionally compromised by the toxicity profile of the procedure necessitating treatment cessation in approximately 1/4 of patients. The 40–50% incidence of i.a.h. fotemustine-induced hepatitis, mostly asymptomatic except in one case, has not been previously observed in the metastatic setting [16], suggesting that healthy liver tissue is more susceptible to the drugs' toxicity than is liver tissue with a macroscopical metastatic involvement.

In summary, the present data provide evidence for the potential role of adjuvant i.a.h. fotemustine for patients at high risk of liver relapse. Nevertheless, its value can only be determined by a large, prospective, randomized trial. However, such a trial might be difficult to perform as patients with locally advanced uveal melanoma are rare, and it would need a large cohort of patients and an international effort. Furthermore, the treatment is associated with several limitations concerning the technical aspect of placing the catheter and a relatively high incidence of treatment-related morbidity. We believe that adjuvant treatments should continue to be studied including new compounds, such as antiangiogenic agents, to substantially improve overall survival of these patients.

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