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ORIGINAL ARTICLE

Cisplatin, gemcitabine and treosulfan is effective in chemotherapy-pretreated relapsed stage IV uveal melanoma patients

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Abstract
Purpose The efficacy of cisplatin, gemcitabine, and treosulfan (CGT) was evaluated in patients with chemotherapy pretreated relapsed AJCC stage IV uveal malignant melanoma.
Methods Patients received i.v./intrahepatic cisplatin, i.v. gemcitabine, and i.v. treosulfan (CGT) on day 1 and 8 as first-line ($n = 1$), second-line ($n = 9$), third-line ($n = 1$) or fourth-line ($n = 1$) therapy. Cisplatin, gemcitabine, and treosulfan (CGT)-therapy was repeated every 5 weeks until progression of disease occurred. A maximum of six CGT-cycles (mean, 2 cycles) was administered per patient.
Results No objective response was observed, six patients (50%) had stable disease and six (50%) patients progressed upon first reevaluation. Overall survival of all the 12 patients was 6 months. Patients with stable disease reached a median overall survival of 12 months, while patients with disease progression upon first reevaluation had a median overall survival of 4 months, only. Grade III/IV related hematotological side effects were experienced in six (leukopenia) and four (thrombocytopenia) patients.
Conclusions Treatment with CGT may lead to disease stabilization and prolonged survival in a substantial proportion of progressive stage IV uveal melanoma patients, even following heavy chemotherapy treatment.

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Introduction

Metastatic uveal melanoma is rare but has a poor prognosis [1,2]. In contrast to cutaneous melanoma, advanced uveal melanoma patients predominantly develop liver metastases (>90%) [3, 4], which are often highly resistant to chemotherapy.

Various cytotoxic agents have been investigated as systemic therapy, among them dacarbazine, BCNU, and combination regimens such as BOLD (bleomycin, vincristine, lomustine, and dacarbazine) leading to response rates less than 1% [2, 5]. Higher response rates and longer response durations have been observed using fotemustine containing regimens and in locoregional approaches with fotemustine or cisplatin-based therapies [4, 6, 7].

Pre-clinical studies on the chemosensitivity of uveal melanoma cells to cytotoxic agents identified tumor sensitivity toward the DNA alkylating agent treosulfan, and synergistic sensitivity when adding the nucleoside analogue gemcitabine to treosulfan [8]. The mechanism of synergy may be best explained by the inhibition of DNA repair mechanisms of the alkylating agent by the nucleotide analogue gemcitabine [9]. In accordance to the in vitro findings, first results of a phase II trial of 24 metastatic uveal melanoma patients treated with gemcitabine and treosulfan showed a prolonged progression-free survival and a slight increase in tumor responses, when compared to 24 patients treated with treosulfan alone [10].

The goal of our present analyses was to evaluate the efficacy of the two alkylating agents cisplatin and treosulfan in combination with gemcitabine mostly in

chemotherapy pretreated relapsed stage IV uveal melanoma patients.

Patients and methods

Patients

Between July 2002 and June 2006, 12 relapsed stage IV uveal melanoma patients received a combination treatment with cisplatin, gemcitabine, treosulfan (CGT).

Criteria for entry into the study were: systemically pretreated relapsed AJCC stage IV uveal malignant melanoma; white blood cell count > 3,500 μl^{-1}; platelet count > 100.000 μl^{-1}; haematocrit > 30%; serum creatinin and bilirubin < 1.5 of the upper normal limit; age between 18 and 80 years and a life expectancy of >3 months. Progressive CNS metastases were no exclusion criteria. Previous systemic cisplatin failures were not excluded, since cisplatin was used in combination, only. All patients had a Karnofsky performance status >80%.

Written informed consent was obtained from all patients prior to therapy.

Treatment design

Treatment was administered first-line ($n = 1$), second-line ($n = 9$), third-line ($n = 1$), or fourth-line ($n = 1$). Patients received 40 mg/m² i.v. cisplatin, 1,000 mg/m² i.v. gemcitabine, and 2,500 mg/m² i.v. treosulfan on day 1 and 8, each. In four patients, cisplatin was administered as single intrahepatic therapy at a fixed dose of 100 mg. Therapy was repeated every 5 weeks until progression of disease occurred.

Ten (83%) patients required a dose reduction due to toxicity. Patients received a mean of two CGT-cycles (range, 1–6) until progression of disease occurred or until last known date to be alive.

Response, survival and toxicity

Maximum response to therapy was evaluated according to World Health Organization (WHO) criteria with regular reevaluation intervals every 2 months by CT scans; complete response: disappearance of all signs of disease for a minimum of 2 months; partial response: 50% or more reduction in the sum of products of the greatest perpendicular diameters of measurable lesions, no increase in lesion size and no new lesions; stable disease: less than a partial response with no disease progression for at least 5 weeks; progressive disease: 25% or more increase in sum of products in the longest perpendicular diameters of measurable lesions or the development of new lesions.

Survival was measured from start of therapy to date of death or to the last known date to be alive.

Maximum toxicity was evaluated according to WHO criteria.

Statistical analysis

The probability of overall survival was plotted over time according to the method of Kaplan and Meier; SPSS software (SPSS Inc., Chicago, IL, USA) was employed.

Results

Median follow-up of all patients was 5.5 months (range, 2–32 months). Patient characteristics are listed in Table 1. The patient group consisted of 11 males and one female, at a median age of 62 years. Stage IV pretreatment consisted of chemotherapy, notably, DTIC, cisplatin, BCNU ($n = 10$), DTIC ($n = 1$), BCNU, bleomycin, vindesine ($n = 1$), and treosulfan, gemcitabine ($n = 1$).

Upon pre-treatment nine patients had stable disease as maximum response while in two pre-treated patients chemotherapy had failed.

Cisplatin, gemcitabine, treosulfan (CGT) therapy was applied as first-line ($n = 1$), second-line ($n = 9$), third-line ($n = 1$), and fourth-line ($n = 1$) therapy, respectively. At start of CGT-therapy, all patients showed progressive metastatic disease at one metastatic site ($n = 9$), two metastatic sites ($n = 2$), and three metastatic sites ($n = 1$), respectively. Metastatic sites were liver ($n = 11$), lung ($n = 1$), bone ($n = 1$), skin/soft tissue ($n = 1$), lymph nodes ($n = 1$), and CNS ($n = 1$).

Outcome

Six patients (50%) had stable disease and six (50%) patients exhibited progressive disease upon first reevaluation (Table 1). There was no difference in response between patients receiving cisplatin intravenously (four stable disease/four progressive disease) and patients receiving cisplatin through the hepatic artery (two stable disease/two progressive disease).

Survival

Overall median survival of all patients was 6 months (95% CI: 4, 8) (Fig. 1a). Patients achieving stable disease ($n = 6$) exhibited a median overall survival of 12 months (95% CI: 0, 24) (Fig. 1b), while patients with disease progression ($n = 6$) upon first reevaluation showed a median overall survival of 4 months (95% CI: 1, 7) (Fig. 1c).

Table 1 Patient characteristics

	CGT
Entered	12
Age (years)	
Median	62
Range	33–73
Sex	
Male	11
Female	1
Stage IV pretreatment[a]	
DTIC, cisplatin, BCNU	10
DTIC	1
BCNU, bleomycin, vindesine	1
Ixoten	1
Treosulfan, gemcitabine	1
Maximum response to stage IV pretreatment	
Stable disease	9
Progressive disease	2
CGT	
First-line	1
Second-line	9
Third-line	1
Fourth-line	1
Sites of progressive metastatic disease	
Liver	11
Lung	1
Bone	1
Skin/soft tissue	1
Lymph nodes	1
CNS	1
Maximum response to CGT therapy	
Stable disease	6
Progressive disease	6

[a] Patients may have had more than one pretreatment

CGT Cisplatin, gemcitabine, and treosulfan, *DTIC* dacarbazine, *BCNU* carmustine

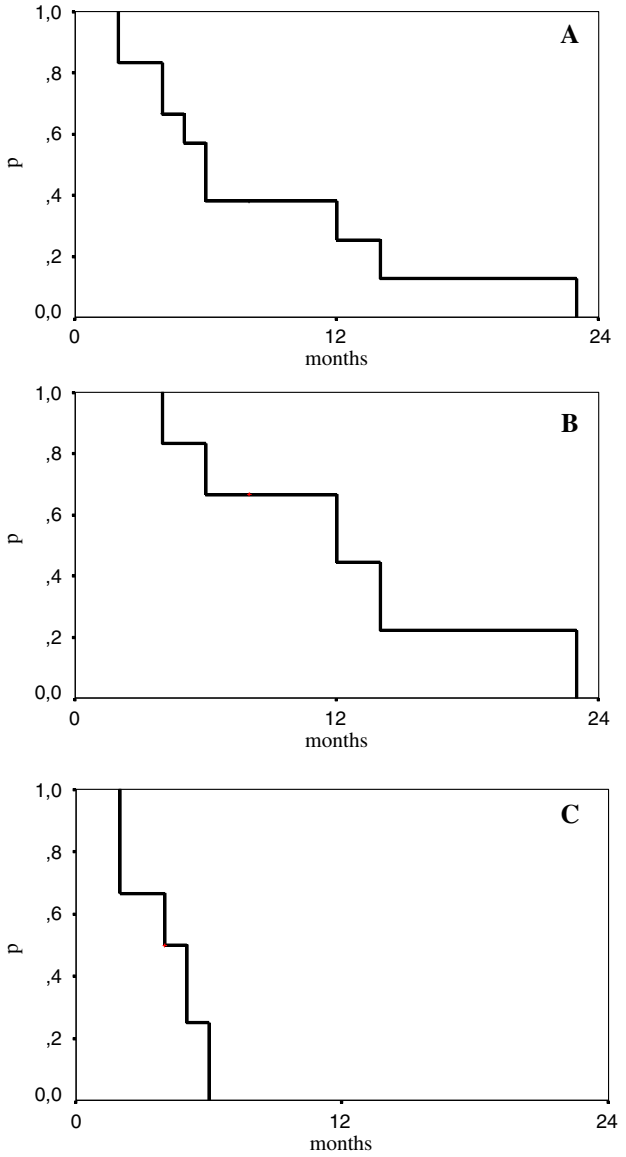

Fig. 1 Overall survival (Kaplan–Meier estimates) of **a** all 12 patients with a median overall survival of 6 months, **b** six patients with partial remission or stable disease and a median overall survival of 12 months, and **c** six patients with progressive disease and a median overall survival of 4 months. Patients were treated with CGT. Survival was measured from start of therapy

At last follow-up, all 12 patients showed disease progression. Six months- and 12 months-progression free survival estimates were calculated at 8%, each (data not shown).

One of 12 patients remains alive with a follow-up of 8 months.

Treatment toxicity

Cisplatin, gemcitabine, treosulfan (CGT) therapy was moderately to well tolerated. No toxic deaths occurred. Hematological side effects such as WHO grades I and II leucopoenia, anemia and thrombocytopenia were observed in five of 12 CGT treated patients, each; grade III or IV leucopoenia and thrombocytopenia were experienced in six and four patients, respectively (Table 2). One patient showed major (WHO grade III/IV) nausea/vomiting.

Discussion

Until today, no standard chemotherapy has been developed for advanced uveal melanoma patients. New strategies for the development of chemotherapy regimens in uveal melanoma arose from in vitro investigations. Pre-clinical studies

Table 2 Hematologic toxicity

Hematologic toxicity[a] WHO criteria	Patients(%)	
	I/II	III/IV
Leucocytopenia	5	6
Thrombocytopenia	5	4
Anemia	5	0

[a] No life-threatening complications and no toxic deaths occurred

CGT Cisplatin, gemcitabine, treosulfan

demonstrated that highly chemoresistent tumor cells, such as uveal melanoma cells, have a synergistic sensitivity to the alkylating agent treosulfan and the nucleotide analogue gemcitabine [8]. Since cisplatin-based chemoembolization through the hepatic artery showed promising results in uveal melanoma patients, we added the alkylating agent cisplatin to the gemcitabine/treosulfan combination.

In our present analysis of 12 high-risk AJCC stage IV uveal melanoma patients mostly failing previous first-, second-, or third-line chemotherapy, six (50%) patients achieved stable disease and six (50%) progressed upon subsequent treatment with the combination of CGT; median overall survival was 6 months.

These results are comparable with findings of a recent study on first-line CGT-treated metastatic uveal melanoma patients [11], and with outcomes of various other systemic (dacarbazine- and cisplatin-based) chemotherapy trials in metastatic uveal melanoma [2, 4, 5].

While higher response rates of 36% (first-line) and 25% (second-line) were observed with intra-arterial cisplatin-based chemotherapy in advanced uveal melanoma [2], our patients responded equally to intravenous (4 SD/4 PD) and intra-hepatic (2 SD/2 PD) cisplatin as a part of the triple drug regimen. In the current patient group, cisplatin was administered intraarterially without embolization to further enhance treatment feasibility and tolerability, although other authors [6] had previously shown promising response rates with embolization.

Notably, while the present CGT therapy resulted in no objective responses in relapsed metastatic uveal melanoma patients, 50% of patients reached stable disease with extended median overall survival of 12 months; a comparable median survival was observed in objective responders after treatment with intra-arterial cisplatin-based chemotherapy [2]. The prolonged survival of stable disease patients, as observed here, was even more striking given the number of prior therapies.

In summary, treatment with CGT may lead to disease stabilization and prolonged survival in a substantial proportion of progressive stage IV uveal melanoma patients, even following heavy chemotherapy treatment.

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Conflicts of interest: All authors disclose any financial and personal relationships with other people or organizations that could inappropriately influence (bias) this work.

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