Original article

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European Organization for Research and Treatment of Cancer (EORTC) open label phase II study on glufosfamide administered as a 60-minute infusion every 3 weeks in recurrent glioblastoma multiforme

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Background: Glufosfamide is a new alkylating agent in which the active metabolite of isophosphoramide mustard is covalently linked to β-D-glucose to target the glucose transporter system and increase intracellular uptake in tumor cells. We investigated this drug in a multicenter prospective phase II trial in recurrent glioblastoma multiforme (GBM).

Patients and methods: Eligible patients had recurrent GBM following surgery, radiotherapy and no more than one prior line of chemotherapy. Patients were treated with glufosfamide 5000 mg/m^2 administered as a 1-h intravenous infusion. Treatment success was defined as patients with either an objective response according to Macdonald's criteria or 6 months progression-free survival. Toxicity was assessed with the Common Toxicity Criteria (CTC) version 2.0.

Results: Thirty-one eligible patients were included. Toxicity was modest, the main clinically relevant toxicities being leukopenia (CTC grade >3 in five patients) and hepatotoxicity (in three patients). No responses were observed; one patient (3%; 95% confidence interval 0 to 17%) was free from progression at 6 months. Pharmacokinetic analysis showed a 15% decrease in area under the curve and glufosfamide clearance in patients treated with enzyme-inducing antiepileptic drugs, but no effect of these drugs on maximum concentration and plasma half-life.

Conclusion: Glufosfamide did not show significant clinical antitumor activity in patients with recurrent GBM.

Key words: chemotherapy, glioblastoma multiforme, glufosfamide, recurrent

Introduction

Despite many trials to improve the outcome of patients with high-grade glioma, the prognosis of this disease remains dismal. In particular, the prognosis of glioblastoma is poor, with a median survival of 9–12 months. Once the tumor recurs following initial treatment further treatment options are limited. Even chemotherapy with temozolomide, recently approved for this indication, offers a low response rate (5–10%) with ~20% of patients remaining free from progression at 6 months after the start of treatment [1, 2]. This shows the clear need for better medical treatment for this disease, which requires the investigation of new and promising agents in well-designed phase II trials.

Glufosfamide is a new alkylating agent in which the active metabolite isophosphoramide mustard is linked to β-D-glucose [3]. Glufosfamide does not require metabolic activation by hepatic microsomal enzymes such as the oxazaphosphorines cyclophosphamide and ifosfamide. There is evidence that the Na-D-glucose cotransporter SAAT1 mediates the transport of glufosfamide into human tumor cells and this mechanism may lead to accumulation of the drug in tumor cells [3, 4]. Together with the elevated metabolic rate and glucose consumption rate of tumor cells, this targeting mechanism probably contributes to the relative selectivity of glufosfamide for tumor cells. The drug was found to be active against the glioblastoma multiforme (GBM)

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cell line HTB 14 (A. R. Hanauske, Baxter Oncology, data on file). In phase I studies renal tubular acidosis and neutropenia were the dose-limiting toxicities. The recommended phase II dose was 4500 mg/m^2 when given as a 6-h infusion or 5000 mg/m^2 when given as a 60-min infusion [4, 5]. In phase I studies evidence of antitumor activity in resistant solid tumors was observed. As part of a broad phase II program to investigate the activity of glufosfamide in solid tumors, the European Organization for Research and Treatment of Cancer (EORTC) New Drug Development Group and Brain Tumor Group investigated this drug in recurrent GBM (EORTC study 16994G-26002).

Patients and methods

Patients were eligible if they had: a histologically proven GBM at first surgery; recurrent or progressive disease after radiation therapy; at least one bidimensionally measurable target lesion requiring a contrast enhancing lesion with a diameter of at least 2 cm on magnetic resonance imaging (MRI) or computed tomography scan; no more than one line of prior chemotherapy, either given adjuvant or at first recurrence; no prior high-dose radiotherapy (>65 Gy), stereotactic radiosurgery or internal radiotherapy; no surgery or radiotherapy within the last 3 months prior to registration; stable or decreasing dose of steroids for at least 1 week; adequate hematological, hepatic and cardiac function; normal renal function as assessed by serum creatinine <150 μmol/l and a creatinine clearance of ≥60 ml/min as determined by the formula of Cockcroft and Gault; World Health Organization (WHO) performance status 0–2; age ≥18 years; given written informed consent. All participating centers obtained approval of the local medical ethical board prior to study activation.

Before the start of treatment all patients were centrally registered at the EORTC Data Center in Brussels. The treatment consisted of glufosfamide 5000 mg/m^2 administered as a 60-min intravenous infusion every 3 weeks, for a minimum of 6 months in case of stabilization of the disease or for at least two cycles after confirmation of an objective response. No nephroprotective hydration schedule was foreseen in these patients. Response was evaluated after every two cycles with MRI scanning.

The primary end point of the study was the success rate. A 'success' was defined as either an objective response according to Macdonald's criteria or absence of progression for at least 6 months [6, 7]. Secondary end points included toxicity, the pharmacokinetic profile of glufosfamide, the estimation of progression-free survival and response duration.

Using the one-step Fleming design, while considering a success rate of <5% as unacceptable, 28 patients were needed to assure with 90% power and a type I error of 10% that if the success rate is ≥20% the regimen can be recommended for further investigation in phase III studies [8]. All analyses were restricted to patients that started treatment. The success rate and its 95% confidence interval (CI) were calculated by pooling, in all eligible patients, those patients with complete response (CR) or partial response (PR) and those patients with stable disease (SD) for at least 6 months. Progression-free survival (PFS), overall survival (OS) and duration of response were to be estimated by the Kaplan–Meier method and calculated from the start of chemotherapy [9]. OS was measured until the date of death or last follow-up examination otherwise. PFS was measured until the first sign of radiological or clinical progression (whichever came first) or death or last follow-up visit otherwise. Toxicity was assessed according to the Common Toxicity Criteria (CTC), version 2.0. The relationship of any toxicity was scored as either likely related to the treatment, unlikely related or relationship not assessable. During cycle one, blood samples for pharmacokinetic analysis were drawn at 0 h (predose), at 1 h (immediately post-infusion), at 3 h and at 8 h.

Results

Between February and August 2001, 32 patients were registered by 12 institutions. Median age was 56 years (range 30–71 years); the WHO performance status was 0 in five patients, 1 in 22 patients and 2 in five patients. Twenty-five patients had received prior chemotherapy, following radiotherapy in 17 patients and at first recurrence in eight patients. One patient was considered ineligible because the serum bilirubin on the day of entry was >1.5 the upper limit of normal. All patients started treatment. A total of 94 cycles were administered (median two cycles; range 1–8).

Most reported toxicities were considered unrelated to the treatment. In four patients (five cycles) retreatment was delayed, which was due to neutropenia (CTC grade 2) in three patients. The relative dose intensity of glufosfamide was between 90% and 110% of the theoretical dose for all patients but one. Grade 3 or 4 hematological toxicity (leukopenia or neutropenia) was observed in six patients (16 cycles). Three patients developed a grade 3 hepatotoxicity, with a predominant increase of alanine aminotransferase and γ-glutamyltransferase. The ineligible patient with a baseline increase in bilirubin (CTC grade 2) developed a grade 3 increase in bilirubin, with full recovery after discontinuation of treatment. One other patient developed a grade 2 creatinine increase with a grade 2 proteinuria. One patient developed a grade 3 infection and one patient grade 3 vomiting. Several grade 3 electrolyte disturbances were observed (hyponatremia, hypo- and hypercalemia, hypermagnesemia, hypophosphatemia) and one grade 4 hypocalemia.

At the time of this report, all but one patient have progressed and 17 patients have died. No responses were observed, 10 patients had no change after two cycles and one patient (3%; 95% CI 0 to 17%) remained free from progression at 6 months.

Four patients were excluded from the pharmacokinetic analysis, because they had erroneously received a nephroprotective hydration schedule which may influence pharmacokinetic parameters. A moderate inter-individual variability was observed in the remaining 27 patients. Table 1 shows pharmacokinetic parameters for all non-hydrated patients. Patients treated with enzyme-inducing antiepileptic drugs (EIAED; carbamazepine, phenytoine, phenobarbital, oxcarbazepine) showed a statistically significant decrease of ~15% of the glufosfamide clearance and the area under the curve (AUC; $P = 0.043$) as compared with patients not using these agents. No significant differences were observed in glufosfamide maximum concentration and plasma half-life time.

Discussion

Glufosfamide showed a low hematological and non-hematological toxicity profile in GBM patients. The relatively large volume that was administrated in a short time (1000 ml in 60 min) did not cause increased edema or neurological deterioration during or shortly after the infusion, events that have been observed in brain tumor patients receiving hydration before cisplatin [10]. The predominant toxicity consisted of neutropenia and hepatotoxicity. In one patient a grade 2 renal toxicity was observed. Glufosfamide was well tolerated in this group of patients. No objective responses were observed, and only one of 31 patients (3%; 95%

Table 1. Results of pharmacokinetic analysis in the 27 non-hydrated patients: mean values (ranges)

	No. of patients	C_{max} (μg/ml)	$t_{½}$ (h)	AUC (μg·h/ml)	Clearance (ml/min/m^2)
All patients	26	479 (382–696)[a]	1.8 (1.3–2.9)	1487 (1086–2204)	57 (38–77)
With EIAED	10	451 (384–500)	1.7 (1.4–2.2)	1341 (1086–1669)	62 (48–77)
Without EIAED	16	495 (382–696)[b]	1.9 (1.3–2.9)	1579 (1114–2204)	54 (38–71)
P value		0.145	0.206	0.043	0.043

[a]Samples from 27 patients included.
[b]Samples from 17 patients included.
AUC, area under the curve; C_{max}, maximum concentration; EIAED, enzyme-inducing antiepileptic drugs; *P* value, difference between patients with and without EIAED; $t_{½}$, terminal half-life.

CI 0 to 17%) remained free from progression at 6 months after the start of treatment. The pharmacokinetic analysis in this study showed overall a profile comparable to results obtained in phase I and II studies in patients with non-neurological solid tumors (data not shown). In the group of patients treated with EIAED, a slight (15%) increase in clearance and AUC was observed. Glufosfamide is not metabolized through interaction with CYP3A4 cytochrome and beforehand no interaction was expected. The differences are small however, especially in view of the more pronounced and clinically relevant interactions observed with paclitaxel and CPT-11 [11, 12]. Whether the presently observed interaction is of clinical relevance remains to be established. Its shows, however, the relevance of pharmacokinetic studies in studies on medical treatment of brain tumors, even if beforehand no interaction is expected.

In studies on primary brain tumors, Macdonald's criteria have been widely accepted as the primary end point [6]. Several recent trials on GBM used the percentage of patients remaining free from progression at 6 months as the primary end point, using a large database with negative phase II trials on GBM as a reference source [1, 2]. The advantage of the latter criterion is that it acknowledges the clinical benefit of SD for a patient with a disease in which a rapidly progressive course is the rule [7, 13]. The use of this criterion also allows comparison to future trials with new agents in which a true response is not to be expected. We felt reluctant to leave out the objective response criterion (partial or complete response) because true responses (partial or complete), regardless of duration, would still imply clinical activity of glufosfamide. We therefore combined both end points and considered as a treatment 'success' any patient in which either a partial or complete response was observed, or in which 6 months PFS was obtained. Unfortunately, only one patient in the present study met these conditions.

In conclusion, treatment with glufosfamide was in general well tolerated but did not show significant activity in GBM. The present study does not support further investigations of glufosfamide in recurrent GBM.

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