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Glufosfamide administered by 1-hour infusion as a second-line treatment for advanced non-small cell lung cancer: a phase II trial of the EORTC-New Drug Development Group☆

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Abstract

The activity of glufosfamide (β-D-glucosylisophosphoramide mustard) was tested in a multicentre phase II clinical trial in patients with advanced non-small cell lung cancer (NSCLC) who had received one prior line of platinum-based chemotherapy. Patients were treated with 5000 mg/m^2 glufosfamide by a 1-h intravenous (i.v.) infusion every 3 weeks following registration at the European Organisation for Research and Treatment of Cancer (EORTC) Data Center. Patients were randomised between hydration and no hydration to evaluate the nephroprotective effects of forced diuresis. Patients experiencing $\geqslant$35 μmol/l increase of serum creatinine compared with baseline values were taken off the treatment. The Response evaluation criteria in solid tumours (RECIST) criteria were applied for the response assessment. Blood sampling was performed for a pharmacokinetic analysis. 39 patients from seven institutions were registered and a median of three cycles was given (range 0–6) cycles; 20 patients were randomised to the hydration arm. Haematological toxicity was mild, but treatment-related metabolic and electrolytic abnormalities and increases of serum creatinine occurred in several patients. Hydration did not have any significant influence on the plasma pharmacokinetics of glufosfamide and did not show any nephroprotective effect. Only one confirmed partial remission was observed (response rate 3%; 95% (Confidence Interval (CI) 0–14) and 18 cases with stable disease (49%) were recorded as assessed by an independent panel. Median survival of all patients treated was 5.8 months (95% CI 4.2–7.9). In conclusion, glufosfamide administered by a 1-h infusion every 3 weeks has modest activity in advanced NSCLC patients after one prior platinum-based chemotherapy.

Keywords: Non-small cell lung cancer; Chemotherapy; Glufosfamide; Phase II

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1. Introduction

Non-small cell lung cancer (NSCLC) represents the most frequent malignancy in Western countries and no major progress in the treatment of advanced disease has been achieved in recent years. Although chemotherapy improves survival over 'best supportive care', this is only by approximately 2 months for the median value, at the expense of substantial toxicity [1]. First-line chemotherapy is usually platinum-based. A number of novel chemotherapeutic agents have been introduced in the past decade, including gemcitabine, the taxanes paclitaxel and docetaxel, and vinorelbine. These agents have consistent activity in this disease. However, recently, the comparison of several platinum-based doublets including these novel agents, did not result in any significant difference in survival endpoints, although there may be differences in the side-effect profiles [2].

Second-line chemotherapy has become more common in recent years and docetaxel has been registered for this indication. Docetaxel was observed to improve survival in comparison with 'best supportive care' [3] or a control of vinorelbine or ifosfamide [4], in two relatively large, randomised studies including platinum pre-treated patients. In these aforementioned studies, the response rate of docetaxel was approximately 7%, and median survival approximately 6–7 months.

Assessment of novel agents in advanced NSCLC has shifted in recent years to inclusion in second or even further lines of therapy, because of the theoretical risk of a detrimental effect on survival if an inactive agent is used in the first-line setting, instead of the usual platinum-based combination. Therefore, many new agents are now being tested after failure on these prior platinum-based therapies [5]. Recently, gefitinib (Iressa), an orally available epidermal growth factor receptor (EGFR) inhibitor has been registered in Japan and the United States (US), for patients with advanced NSCLC relapsing after platinum-based chemotherapy and docetaxel.

Ifosfamide has definite activity in advanced NSCLC, and it is usually employed in combination in first-line therapy. Glufosfamide, an ifosfamide derivative, is a compound that has the directly active alkylating moiety isophosphoramide mustard linked to β-D-glucose which gives it the potential to exploit the transmembrane transport system of glucose [6]. It has been shown that glufosfamide is conveyed into tumour cells by SAAT1, a low affinity sodium/glucose co-transporter, while other glucose transporters may also play a role in the intracellular translocation of this compound [7]. Together with the accelerated metabolic rate and glucose consumption of the tumour cells, this targeting mechanism probably contributes to the tumour selectivity for the study drug. A major advantage of glufosfamide over ifosfamide is that glufosfamide does not require mesna to protect from urothelial toxicity. However, some renal toxicity was observed in phase I studies, and this prompted us to use active hydration to try to prevent the associated nephrotoxicity.

We report here, the results of an European Organisation for Research and Treatment of Cancer (EORTC) phase II study of glufosfamide as second-line chemotherapy in patients with advanced NSCLC.

2. Patients and methods

2.1. Study design — objectives

This trial was a prospective, multicentre randomised phase II trial conducted by the EORTC New Drug Development Group and monitored by the EORTC Data Center (EORTC Trial 16994N). The primary objective of the trial was to determine the antitumour activity of glufosfamide in advanced NSCLC patients pretreated by chemotherapy. Secondary objectives were to determine the duration of objective responses, to characterise the toxicities and assess the impact of forced diuresis on renal toxicity in patients treated with a 1-h infusion of glufosfamide, every 3 weeks. Another objective was to further characterise the pharmacokinetic profile of glufosfamide. Patients were randomised to receive hydration versus no hydration. Dose and schedule were selected on the basis of the results of two phase I trials that investigated glufosfamide at two different schedules of administration. In the first study, glufosfamide was administered as a short 30–60 min infusion, every 3 weeks (unpublished data on file). The second trial evaluated a 6-h biphasic infusion schedule [8]. Since neither toxicity nor antitumour activity recorded in the two trials favoured one schedule, the short infusion schedule was selected for practical reasons.

2.2. Registration procedures

To be considered eligible for the trial, patients had to fulfil the following criteria: histologically- or cytologically-proven advanced NSCLC not amenable to curative therapy, one prior platinum-based chemotherapy was allowed, at least one measurable target lesion, Eastern Cooperative Oncology Group (ECOG) performance status $\leqslant 2$, life expectancy $\geqslant 3$ months, use of effective contraception, normal haematological function assessed by absolute neutrophil count (ANC) $\geqslant 1.5\times10^9$/l, platelets $>100\times10^9$/l, normal liver function, serum creatinine $\leqslant 150$ μmol/l and creatinine clearance $\geqslant 1$ ml/s (calculated by the Cockcroft and Gault formula), normal cardiac function without history of ischaemic heart disease or congestive heart failure in the past 6 months and normal 12-lead electrocardiogram (ECG).

Patients with symptomatic brain metastases were excluded. Patients signed a written informed consent before registration. Registration and randomisation were performed centrally (EORTC Data Center, Brussels, Belgium).

2.3. Treatment regimen

Patients in this trial received 5000 mg/m^2 glufosfamide diluted in 1000 ml NaCl 0.9% and administered intravenously (i.v.) over 60 min, every 3 weeks. Treatment was continued up to six cycles in responding or stable patients or until progressive disease, unacceptable toxicity or patient refusal.

Patients were randomised to receive hydration or no hydration. Hydration consisted of 4 additional litres of fluids: 2 l of glucose 5% and NaCl 0.9% (1:1) plus 20 mEq KCl per litre in 4 h prior to, and again following, completion of administration of the glufosfamide solution.

2.4. Clinical evaluation

Before registration, the following tests were performed: blood cell counts, chemistries, urinalysis, ECG, chest X-ray and adequate imaging techniques were utilised in order to properly assess the tumour extent. Patients were observed weekly, and haematology and chemistries were repeated weekly and before each cycle. Tumour response was assessed every two cycles while on treatment and thereafter every 6 weeks until progression. The Response evaluation criteria in solid tumours (RECIST) were applied. Response to the treatment was evaluated independently by an expert radiologist. Overall survival and progression-free survival were estimated by the method of Kaplan–Meier and calculated from the date of the start of chemotherapy. Survival was measured until the date of death or was censored at the follow-up date. Duration of response was measured from the date of first response and was observed until the first sign of progression. Toxicity was assessed according to the international Common Toxicity Criteria version 2 (published 30 April 1999) [9].

Patients experiencing an increase of serum creatinine (0.4 mg/dl or 35 μmol/l) measured twice over a 1-week period compared with baseline value, went off the study. The dose of glufosfamide was reduced by 25% in cases of febrile neutropenia. The dose was postponed in cases of persistent grade 2 toxicity at the time of the next cycle, up to a maximum of 2 weeks.

2.5. Statistics

The two-stage Simon design was used for the sample size determination and the decision rule regarding the response rate. In the first step, 16 patients were needed to assure with a 95% power and a type I error of 20% that if the true response rate is 5%, the study had to be stopped. If one or more responses were observed, then 16 more patients would be enrolled to show that if the true response rate is 20%, the regimen can be recommended for further investigation in phase III studies.

2.6. Pharmacokinetics

Heparinised blood (5 ml each) was collected from patients during the first treatment course at the following time points: 0 h (pre-dose), 1 h (end of infusion), 3 and 8 h and the plasma was extracted. The plasma samples were stored deep-frozen and shipped on dry ice to the analytical site, where samples were stored at −20 °C until analysis. Analyses of plasma samples were performed by a validated high performance liquid chromatographic-mass spectrometry (HPLC-MS) method that employs chromatographic separation and mass spectrometric detection (Analytico Research B.V., 1998, 2000). All test samples and QC samples were generally analysed after a 10-fold dilution. The lower limit of quantification for the determination of glufosfamide was 1 μg/ml, with a limit of detection of 0.5 μg/ml (after the 10-fold dilution).

The measured plasma concentrations were evaluated by non-compartmental pharmacokinetic analysis with a validated Excel based software (FUNCALC 2, 2001). For statistical analysis of pharmacokinetics, an ANOVA model with the factors hydration, gender and hydration∗gender was fitted to the log-transformed pharmacokinetic parameters maximal concentration (C_{max}), half-life ($t_{1/2}$), area under the curve (AUC) and clearance (CL). The mean square errors obtained in this model were used to calculate 90%-Confidence Intervals (CIs) for the expected difference and after re-transformation for the expected ratio in parameters between hydrated and non-hydrated patients, as well as between male and female patients.

3. Results

Between February 2000 and February 2001, 39 patients were entered onto the trial from seven institutions. 19 patients were randomised to the no-hydration arm and 20 to receive hydration. One patient randomised in the no-hydration arm did not start treatment and was excluded from the evaluation. One patient was found to be ineligible because of the absence of measurable disease. The main characteristics at study entry of the 38 patients who underwent treatment are listed in Table 1. Most patients had stage IV disease, adenocarcinoma histology and were male. Approximately one quarter had a performance status of 2.

A total of 120 cycles were given (median of three cycles per patients, range 0–6 cycles), and 8 patients (21%) completed six cycles of glufosfamide therapy.

There were no dose reductions and treatment was delayed in seven cycles, due to haematological toxicity in 1 case and in 6 cases the delays were not related to toxicity.

The main reason for stopping treatment was progression of disease in 56 and 60% of the two arms (no hydration and hydration arms, respectively). 5 and 2 patients, respectively, stopped treatment because of toxicity. 4 patients in the hydration arm stopped treatment due to a general worsening of their performance status.

The relative dose intensity approached 100% in both arms (99.2 and 100% in the no hydration versus hydration arm). Table 2 gives details of grade 3 and 4 haematological toxicities. One-third of patients had grade 3-4 neutropenia in the no-hydration arm and 10% had grade 3 neutropenia in the hydration arm. One patient had febrile neutropenia in the no-hydration arm, and 1 patient had grade 3 thrombocytopenia in the hydration arm.

Table 1
Patient's characteristics

	Treatment	
	No hydration ($N=18$)	Hydration ($N=20$)
Age (years)		
Median (range)	58.7 (3.74–74.1)	60.8 (39.7–74)
Gender		
Male	14 (78)	13 (65)
Female	4 (22)	7 (35)
Performance status (WHO)		
0	5 (28)	2 (10)
1	9 (50)	12 (60)
2	2 (22)	6 (30)
Histological subtype		
Squamous cell	6 (33)	4 (20)
Adenocarcinoma	9 (50)	12 (60)
Mixed adenosquamous	1 (6)	1 (5)
Large cell undifferentiated	2 (11)	3 (15)
Stage of disease		
IIIa	1 (6)	1 (5)
IIIb	1 (6)	3 (15)
IV	16 (89)	16 (80)
Surgery[a]		
No	11 (61)	15 (75)
Yes, curative	4 (22)	3 (15)
Yes, others	3 (8)	2 (5)
Radiotherapy		
No	7 (39)	9 (45)
Yes	11 (61)	11 (55)
Chemotherapy		
Yes, adjuvant only	2 (11)	2 (10)
Yes, for advanced disease	16 (89)	18 (90)

WHO, World Health Organization.
[a] Some data are missing in this subgroup.

Elevation of creatinine by more than 35 μmol/l occurred in 9 patients (24%), often at the end of the treatment period.

Non-haematological toxicities are described in Table 3. Fatigue was a common side-effect, although this symptom was not clearly related to the toxicity of the drug. Grade 3 nausea and vomiting was observed in a few patients and at similar levels in the two arms. One patient in both arms developed a grade 3 proteinuria. Grade 3 and 4 renal failure was observed in 2 patients in the hydration arm. There appeared to be no effect of hydration in preventing renal function disturbances. 6 patients (2 in the hydration arm and 4 in the no-hydration arm) developed hypophosphataemia. No major differences in toxicity were observed between the hydration and no hydration arms, although the relatively small number of patients included may preclude definite conclusions.

One patient, randomised in the hydration arm, was considered ineligible because of the absence of measurable lesions. Three patients were not assessable. According to the RECIST criteria for tumour response, only one patient attained the definition of a confirmed partial response (1/37, response rate 3%, 95% CIs 0–14) based on all eligible patients who started therapy. This evaluation was provided by an independent radiology review, which did not confirm the two other responses that were claimed by investigators. For this reason, the sample size was larger than initially anticipated in our statistical design. 18 patients had stable disease and 15 progressive disease. The partial response lasted 4 months and 5 days. Overall median survival was 5.8 months (95% CI 4.2–7.9), and median progression-free survival was 2.5 months (95% CI 1.3–3.9).

3.1. Pharmacokinetics

The individual plasma concentration–time courses showed moderate inter-individual variability. This study provided adequate pharmacokinetic analysis in a multicentre setting. Table 4 shows the medians and ranges for the main pharmacokinetic parameters. There was a

Table 2
Haematological toxicity. Number of patients (%)[a]

Grade	No hydration arm		Hydration arm	
	3	4	3	4
Leuvocytes	5 (28)	0	2 (10)	0
Neutrophils	4 (22)	2 (11)	2 (10)	0
Platelets	0	0	1 (5)	0
Haemoglobin	0	0	1 (5)	0

[a] In the hydration arm, one cycle was not documented for the haematological toxicity and biochemistry data for 1 patient because of early death due to progression of the disease after first treatment administration.

Table 3
Non-haematological toxicity: number of patients (%)

Grade	Hydration arm ($n=20$)				No hydration arm ($n=18$)			
	1	2	3	4	1	2	3	4
Fatigue	0	5 (25)	3 (15)	0	2 (11)	4 (22)	1 (6)	0
Acidosis	0	0	0	0	1 (6)	0	1 (6)	0
Alopecia	4 (20)	6 (30)	0	0	4 (22)	5 (28)	0	0
Diarrhoea	3 (15)	1 (5)	0	0	0	0	0	0
Nausea	5 (25)	8 (40)	1 (5)	1 (5)	5 (28)	7 (39)	1 (6)	0
Vomiting	7 (35)	5 (25)	2 (10)	0	7 (39)	6 (33)	1 (6)	0
Other neurological	2 (10)	1 (5)	0	0	0	0	0	0
Febrile neutropenia	0	0	0	0	0	0	1 (6)	0
Renal failure	0	0	1 (5)	1 (5)	1 (6)	0	0	0
Proteinuria	0	1 (5)	1 (5)	0	4 (22)	1 (6)	1 (6)	0

Table 4
Pharmacokinetic parameters

		Pharmacokinetic parameter			
		C_{max} (μg/ml)	$T_{1/2}$ (h)	AUC (μg h/ml)	CL (ml/min/m^2)
Hydration group					
	n	18	16	16	16
	Median (range)	320.2 (237–431)	2.1 (1.28–3.19)	995.3 (646–1335)	87.5 (61.6–132.3)
No-hydration group					
	n	17	18	18	18
	Median (range)	402.7 (236–653)	1.94 (1.47–3.3)	1191.4 (716.7–2017)	70 (41.3–116.3)

tendency for lower plasma concentrations and higher CL values in the patients who received hydration. However, these differences were not significant. There was no effect of gender on any of the parameters examined.

4. Discussion

Second-line chemotherapy has become more common in recent years. A large number of patients who relapse on first-line platinum-based chemotherapy have a relatively good performance status allowing them to be candidates for further chemotherapy. Activity of second-line cytotoxic therapy in advanced NSCLC is poor, with response rates rarely exceeding 10% [5]. Docetaxel was registered based on two randomised studies showing improved survival in comparison with best supportive care or two inactive cytotoxics [3,4]. In the study by Shepherd and colleagues [3], the response rate to docetaxel was 7.1% and the median survival was 7 months. In Fossella's study [4], the response rate to 75 mg/m^2 docetaxel was 6.7%. It was 10.8% in the 100 mg/m^2 arm of this study and 0.8% in the other arm (which included vinorelbine or ifosfamide); median survival was 5.7 months in the 75 mg/m^2 docetaxel dose group. Patients in these studies were more heavily pretreated than in our present study, and both response rates and median survivals appear to be somewhat better compared with our study. Although it is very hard to compare non-randomised series of patients enrolled in different studies, it does not appear that glufosfamide would substantially challenge current second-line treatment for advanced NSCLC.

Although ifosfamide has shown important activity in first-line therapy in advanced NSCLC, in a second-line randomised study by Fossella and colleagues [4], the response rate was lower than 1%. Glufosfamide might provide some advantages to ifosfamide treatment, but the results of our present study do not support further investigation of its use as second-line treatment for NSCLC.

Furthermore, the renal toxicity of glufosfamide appears to be unpredictable and not easily prevented by hydration. This may be an important drawback to the use of this drug in patients who have already received potentially nephrotoxic drugs, such as cisplatin. This side-effect would also restrict the combination of glufosfamide with other agents such as platinum analogues, which are often used as first-line drugs.

Of note, hydration did not significantly impact on the main pharmacokinetic parameters analysed in our study.

The recent introduction of targeted therapies, such as EGFR inhibitors, in recurrent NSCLC has made the development of cytotoxics in this setting less attractive.

Gefitinib (Iressa™) and Erlotinib (Tarceva™) have both shown response rates in the range of 10–20% in the second-line or further lines of therapy NSCLC, and are tolerated better by the patients than chemotherapy [10,11]. It is expected that these agents will be increasingly used instead of chemotherapy in relapsing patients with advanced NSCLC.

In conclusion, glufosfamide does not seem to have sufficient activity to support its further development as second-line therapy for advanced NSCLC. Its toxicity profile is such that it cannot be easily combined with other cytotoxics used in the first-line setting.

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