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ORIGINAL ARTICLE

A Phase 1 dose-escalation trial of glufosfamide in combination with gemcitabine in solid tumors including pancreatic adenocarcinoma

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Absract
Purpose To evaluate safety and pharmacokinetics and to establish the maximum tolerated dose of glufosfamide when administered in combination with gemcitabine in advanced solid tumors.
Methods This Phase 1 dose-escalation study evaluated the combination of glufosfamide + gemcitabine in patients with advanced solid tumors. Cohorts of three to six patients were treated with glufosfamide doses from 1,500 to 4,500 mg/m^2 IV over 4 h on Day 1 and gemcitabine 1,000 mg/m^2 IV over 30 min on Days 1, 8 and 15 of every 28-day cycle. Detailed PK sampling was performed on days 1 and 8 of the first two cycles.
Results Nineteen patients were enrolled. Two patients had dose-limiting toxicity: Grade 3 fatigue at 2,500 mg/m^2 and Grade 4 thrombocytopenia at 4,500 mg/m^2. Five patients completed six cycles and one patient remained on study for ten cycles. Two patients discontinued for adverse events. Grade 3/4 neutropenia and thrombocytopenia occurred in seven patients and five patients, respectively. The CrCL fell below 60 mL/min in two patients. There was one unconfirmed partial response and 10 of 19 (52.6%) patients had stable disease or better at 8 weeks and three patients had continuing stable disease at 24 weeks. Pharmacokinetic analyses suggest no interaction between glufosfamide and gemcitabine.
Conclusion Phase I data indicate that full dose glufosfamide (4,500 mg/m^2) can be given safely in combination with gemcitabine. A Phase II study in patients with pancreatic adenocarcinoma is ongoing.

Keywords Pancreatic cancer · Phase I · Combination chemotherapy · Gemcitabine · Glufosfamide · Targeted therapy

Introduction

Glufosfamide (Threshold Pharmaceuticals, Redwood City, CA) is a new cytotoxic alkylating agent prodrug in which isophosphoramide mustard (IPM) is glycosidically linked to β-D-glucose. The active IPM is released by intracellular glucosidases or by hydrolysis after transport across the cell membrane [13]. The structure and metabolism of the glufosfamide molecule may result in two advantages: less toxic metabolites than ifosfamide and tumor targeting through the glucose moiety to rapidly proliferating tumor cells that have increased glucose consumption compared to normal cells.

The metabolic activation of the prodrug glufosfamide by intracellular glucosidases is not accompanied by the release of the toxic metabolite acrolein, which has been shown to cause hemorrhagic cystitis in patients treated with ifosfamide [4]. Moreover, the amount of metabolically generated toxic chloroacetaldehyde after administration of glufosfamide is significantly lower than with ifosfamide (unpublished data).

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Although the pathogenesis of ifosfamide-induced nephrotoxicity and neurotoxicity are poorly understood, reductions in chloroacetaldehyde production may minimize these toxicities.

Malignant cells utilize glucose at a higher rate than normal cells and express higher levels of glucose transporters, which may lead to preferential uptake of glufosfamide by malignant cells. Glufosfamide has been evaluated as a single-agent in phase I and II in solid tumors, and in one ongoing phase III trial for patients with previously-treated advanced pancreatic cancer [2, 3, 7]. Dose limiting toxicities in phase I studies of 1-h and 6-h infusions were neutropenia and nephrotoxicity (usually renal tubular acidosis). The recommended phase II doses of single-agent glufosfamide were 5,000 and 4,500 mg/m^2 for 1-h and 6-h infusions, respectively, once every 3 weeks. Glufosfamide has demonstrated activity in various cancers including pancreatic, colon, breast, and non-small cell lung cancer [2].

Tumor xenograft studies (HS766-T, and MiaPaCa-2) revealed significant tumor growth inhibition with glufosfamide alone, and enhanced inhibition when glufosfamide was combined with gemcitabine (unpublished).

Gemcitabine (2′,2′-difluoro-2′-deoxycytidine, Gemzar [Lilly, Indianapolis, IN]) is a pyrimidine analogue with activity against a variety of malignancies including pancreatic cancer [5, 6, 8, 9]. A phase II study of first-line glufosfamide in pancreatic cancer showed similar activity to historical gemcitabine data (median survival 5.3 months and response rate of 5.9%) [3]. This and the results of the xenograft studies noted above prompted interest in exploring the activity of the combination gemcitabine plus glufosfamide in solid tumors, and particularly in patients with pancreatic adenocarcinoma.

The phase I dose-escalation portion of this trial was designed to determine the maximum tolerated dose (MTD) of glufosfamide in combination with standard dose gemcitabine in advanced solid tumors. In addition, the pharmacokinetics (PK), safety, tolerability and preliminary efficacy of this regimen were analyzed. The phase II portion of this trial for first line therapy of advanced pancreatic adenocarcinoma will be reported separately.

Patients and methods

Patient selection

Patients had to have pathologically confirmed locally advanced or metastatic solid tumors, previously treated with at least one chemotherapy regimen or with no standard effective treatment available. Patients must have recovered from reversible toxicities of prior therapy, Karnofsky performance status (KPS) $\geq$ 70, adequate organ reserve including hematopoietic, hepatic and renal function (creatinine clearance [CrCL] $\geq$ 60 mL/min calculated by the Cockcroft–Gault formula) and at least one target or non-target lesion by RECIST [12].

Patients were excluded from the study if they had previously received gemcitabine, if they had symptomatic brain metastases, radiation therapy within 28 days or other antitumor therapy within 21 days before study start. All participating patients signed an informed consent form reviewed and approved by local institutional review boards.

Study design

This was a phase I dose-escalation study to establish the MTD of glufosfamide administered every 28 days in combination with standard dose gemcitabine administered weekly for 3 weeks of every 4 week cycle. Glufosfamide was administered intravenously over 4 h on day 1 of every 4-week cycle. Glufosfamide doses started at 1,500 mg/m^2 and escalated to 2,500, 3,500 and 4,500 mg/m^2 in cohorts of three patients per dose level. Gemcitabine dosing was fixed at 1,000 mg/m^2 (30-min intravenous infusion) on days 1, 8 and 15 of every 4-week cycle. On day 1 of each cycle, gemcitabine was started 30 min after completion of the glufosfamide infusion. A standard "3 + 3" design was used [11]. If one of three patients experienced dose-limiting toxicity (DLT), the cohort was expanded to six patients. If there was no DLT, the dose was escalated for the next cohort of three patients. If 2 DLTs occurred at a dose level, then the previous dose was considered the MTD and dose escalation terminated.

Safety assessments

Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria CTCAE version 3.0. Dose-limiting toxicity was defined as any of the following events related to glufosfamide or gemcitabine during the first cycle: grade 3 or 4 non-hematologic toxicity (excluding nausea/vomiting not adequately treated with anti-emetics and grade 3 transaminase elevation lasting 7 days or less), grade 4 neutropenia lasting 5 days or more, grade 4 thrombocytopenia (or any requirement for platelet transfusion), and unexplained grade 4 anemia.

Serum chemistry and hematology testing were performed before every dose of study drug. Urinalysis was performed before the start of each cycle. If CrCL fell below 60 mL/min, patients were discontinued from the study.

Pharmacokinetics

Plasma samples for analysis of glufosfamide, IPM, gemcitabine and 2′, 2′-difluoro-2′-deoxyuridine (dFdU; the primary inactive metabolite of gemcitabine) were collected at the following times on days 1 and 8 of cycles 1 and 2:

Glufosfamide and IPM: Predose, 15 and 30 min, and 1, 1.5, 2, 3, 4, 4.25, 4.5, 5, 6, 8, 12, 16 and 24 h after start of glufosfamide infusion (day 1)
Gemcitabine and dFdU: Predose, 15, 30, 40 and 50 min, and 1, 1.5, 3.5, 7.5, 11.5 and 19.5 h after start of gemcitabine infusion (days 1 and 8)

All analytes were extracted from human plasma by protein precipitation and analyzed with a validated assay using liquid chromatography with tandem mass spectrometric detection (unpublished data) at Covance Bioanalytical Services (Indianapolis, IN). The lower limit of quantitation was 5.00 ng/mL for both glufosfamide and IPM and 50.0 ng/mL for both gemcitabine and dFdU.

Pharmacokinetic parameters were computed from plasma drug concentrations using standard noncompartmental methods with WinNonlin v. 5.0.

Efficacy assessments

Tumor assessments were performed at baseline and at the end of every other cycle of treatment (every 8 weeks) until disease progression or study discontinuation.

Statistical analysis

The primary objectives of the study were to evaluate the safety and tolerability and to determine the MTD of glufosfamide when administered in combination with gemcitabine at standard doses. Secondary objectives were to evaluate the pharmacokinetics of glufosfamide (including IPM) and gemcitabine (including dFdU) when given in combination and to assess the preliminary anti-tumor activity of this combination as measured by response rate.

Results

Patient population

Nineteen patients were enrolled from December 2004 to December 2005 at three US centers. All patients received at least one dose of glufosfamide and gemcitabine. Patient characteristics are summarized in Table 1. The median time on study was 4 cycles (16 weeks). Five patients completed all 6 cycles and 14 patients discontinued from the study early. Two patients completed more than 6 cycles: one patient with ovarian cancer and one patient with breast cancer remained on study for 8 and 10 cycles, respectively. Reasons for early discontinuation include progressive disease (PD; 11), clinical deterioration without objective documentation of progression (1), adverse event (1), and death due to an adverse event (1).

Table 1 Patient characteristics (n = 19)

Sex (M/F) (N)	9/10
Age (years)	
Median	57
Range	36–69
Karnofsky performance status at screening (N)	
100	2
90	8
80	8
70	1
Previous treatment (N)	
Chemotherapy (1, 2, 5 regimens)	7 (3,3,1)
Other systemic therapy	2
Radiotherapy	4
Surgical resection	8
None	9
Tumor type (N)	
Pancreatic cancer	8
Gallbladder cancer	4
Gastric/duodenal	2
Hepatocellular (fibrolamellar)	1
Breast	1
Ovarian	1
Renal	1
Synovial sarcoma	1
Months since diagnosis of advanced/metastatic disease	
Median	2.3
Range	0.5–56.8
Months since last progression	
Median	0.6
Range	0.1–2.3
Sites of metastatic disease (N)	
Visceral	15
Soft tissue	3
None	1

Toxicity

The MTD of glufosfamide in combination with gemcitabine was not reached in this study. Because 4,500 mg/m^2 is the recommended dose for glufosfamide monotherapy, this dose level was not escalated further. Treatment and DLT are summarized in Table 2. Four patients were treated at 3,500 mg/m^2 because one patient did not complete Cycle 1 due to serious adverse events unrelated to study drug.

One of six patients at dose level 2,500 mg/m^2 had a DLT with grade 3 fatigue 2 days after the first dose of study drug. This patient improved and remained on study for 2 cycles before discontinuing for PD. One of six patients at dose level 4,500 mg/m^2 had DLT with grade 4 thrombocytopenia on

Table 2 Glufosfamide treatment and DLT

GLU dose level (mg/m^2)	Number of patients	Median number of cycles	Range of cycles	Number of DLTs
1,500	3	5	2–8	0/3
2,500	6	5	2–6	1/6
3,500	4	2	1–6	0/4
4,500	6	3	2–10	1/6

cycle 1 day 15. This patient with heavily pretreated metastatic breast cancer continued dose-reduced treatment with 3,500 mg/m^2 of glufosfamide and 500 mg/m^2 of gemcitabine, and maintained stable disease (SD) for 10 cycles.

Fifteen serious adverse events occurred in eight patients, one of which was considered to be related to glufosfamide and gemcitabine (hospitalization for grade 2 vomiting). One patient died from a serious adverse event. This patient had bleeding from pancreatic tumor eroding into the duodenum 31 days after the last dose of glufosfamide and 24 days after the last dose of gemcitabine and died from an iatrogenic bowel perforation at the time of endoscopy. Platelet count at the time of the event was normal. This was not considered a DLT because it was not related to study drugs.

At data cut-off, 18 patients had died. The cause of death was progressive disease in 17 patients and an adverse event (bowel perforation) in one patient. There were no treatment-related deaths.

One patient treated at 3,500 mg/m^2 and two patients treated at 4,500 mg/m^2 required a glufosfamide dose reduction for study drug-related adverse events (neutropenia and thrombocytopenia) during the first cycle. There were no other glufosfamide dose reductions. Nine patients had glufosfamide dose delays because of adverse events, including three for study drug-related adverse events (neutropenia, thrombocytopenia, fatigue, hypophosphatemia). Ten patients required a gemcitabine dose reduction (one at 1,500 mg/m^2, three at 2,500 mg/m^2, and six at 4,500 mg/m^2 glufosfamide), eight of which were for study drug-related adverse events. Of the eight patients who received gemcitabine again after a dose reduction, it was possible to re-escalate the dose to 1,000 mg/m^2 in six of them. Fifteen patients required gemcitabine dose delays or omissions, nine of which were for study drug-related adverse events that usually occurred at day 15.

Hematologic toxicity was common (Table 3). Thrombocytopenia increased with consecutive doses of gemcitabine within a cycle but resolved by the start of the next cycle. Neutropenia was most common in the first cycle and resolved without cycle delay in most patients. Anemia was common at baseline (50% grade 1/2) and generally became worse while on study.

Non-hematologic adverse events are summarized in Table 4. The most common non-hematologic toxicities were nausea, vomiting and fatigue but most cases were grade 1 or 2. Grade 3/4 non-hematologic adverse events occurring in more than one patient were fatigue, small bowel obstruction, hypokalemia, hyperbilirubinemia, alanine aminotransferase increase, alkaline phosphatase increase, deep venous thrombosis and pulmonary embolism, occurring in two patients each. There was no evidence of any treatment-related neurotoxicity in this study. One

Table 3 Hematologic toxicity

MedDRA preferred term	Glufosfamide dose level number of subjects (%)				
	1,500 mg/m^2 (N = 3)	2,500 mg/m^2 (N = 6)	3,500 mg/m^2 (N = 4)	4,500 mg/m^2 (N = 6)	Total (N = 19)
Thrombocytopenia					
Grade 1	1	3	0	1	5 (26.3)
Grade 2	0	0	1	1	2 (10.5)
Grade 3	0	1	0	1	2 (10.5)
Grade 4	1	1	0	1	3 (15.8)
Neutropenia					
Grade 1	0	1	0	1	2 (10.5)
Grade 2	1	2	0	1	4 (21.0)
Grade 3	1	1	1	1	4 (21.0)
Grade 4	0	0	1	2	3 (15.8)
Anemia					
Grade 1	0	1	0	2	3 (15.8)
Grade 2	3	4	4	2	13 (68.4)
Grade 3	0	1	0	2	3 (15.8)
Grade 4	0	0	0	0	0

Table 4 Non-hematologic adverse events reported in at least four subjects

MedDRA preferred term	Glufosfamide dose level number of subjects (%) all events [grade 3/4 events]				
	1,500 mg/m^2 (N = 3)	2,500 mg/m^2 (N = 6)	3,500 mg/m^2 (N = 4)	4,500 mg/m^2 (N = 6)	Total (N = 19)
Nausea	2	6 [1]	2	3	13 (68.4) [1 (5.3)]
Vomiting	3	6 [1]	0	4	13 (68.4) [1 (5.3)]
Fatigue	1	4 [2]	2	3	10 (52.6) [2 (10.5)]
Anorexia	1	3	1	3	8 (42.1)
Abdominal pain	3 [2]	3	1	0	7 (36.8) [2 (10.5)]
Constipation	2	2	2 [1]	1	7 (36.8) [1 (5.3)]
Hypokalemia	0	2 [1]	2	3 [1]	7 (36.8) [2 (10.5)]
Peripheral edema	2	4	0	0	6 (31.6)
Insomnia	2	2	1	1	6 (31.6)
Pruritis	2	1	0	3	6 (31.6)
Pyrexia	0	5	1	0	6 (31.6)
Alopecia	1	2	0	3	6 (31.6)
Cough	1	1	0	3	5 (26.3)
Diarrhea	2 [1]	2	0	1	5 (26.3) [1 (5.3)]
Dyspnea	0	2 [1]	1	2	5 (26.3) [1 (5.3)]
Dysgeusia	1	1	0	2	4 (21.1)
Urinary tract infection	0	2	0	2 [1]	4 (21.1) [1 (5.3)]
Weight decreased	1	2	1	0	4 (21.1)

patient developed grade 2 somnolence on the first day of the study that was attributed to concomitant medications.

Mean CrCL at baseline and at end of study were 110 and 99 mL/min, respectively. One patient with renal cell carcinoma with a previous nephrectomy treated in the 2,500 mg/m^2 cohort had a decline in CrCL from baseline 71 to 55 mL/min after 4 cycles, requiring early study termination per protocol criteria. The patient with breast cancer who was treated for 10 cycles had a decline in CrCL from 70 to 56 mL/min during the 8th cycle, but it returned to baseline before cycle 9 and was 67 mL/min at study termination. Median change in CrCL from baseline to lowest value per dose of glufosfamide was −5.5 mL/min.

Because glufosfamide-associated nephrotoxicity is most commonly due to proximal renal tubular injury, serum phosphorus and urine protein by dipstick were evaluated as potential indicators of renal tubular injury. Four patients developed grade 3 hypophosphatemia (two at 2,500 and one each at 3,500 and 4,500 mg/m^2) and three of these patients had a drop in CrCL:71–55, 123–84, and 70–56 mL/min. Six patients developed 3+ proteinuria on study. Acidosis did not develop in any patient. No patients developed hemorrhagic cystitis.

Six patients developed grade 3/4 hyperbilirubinemia or grade 3 elevated transaminases while on study; these were probably related to study drugs in two patients (transient for 2 weeks), while four patients had documented biliary obstruction due to disease.

Pharmacokinetics

PK data showed no accumulation of glufosfamide or its metabolite, isophosphoramide mustard (IPM) following once every 28 days dosing, as demonstrated by the similar pharmacokinetics of glufosfamide between Cycles 1 and 2. As a result, the data from Cycles 1 and 2 were integrated and are summarized by dose group (Fig. 1). Glufosfamide and IPM both exhibited linear pharmacokinetics between 1,500 and 4,500 mg/m^2 with half-lives of approximately 2–3 h. Glufosfamide has a low mean steady-state volume of distribution (VD_{ss}; mean ± SD) of 11.8 ± 2.7 L/m^2 and low clearance of 5.1 ± 1.0 L/h/m^2 that were both similar across dose groups. In the 4,500 mg/m^2 cohort, the mean maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC) of glufosfamide were 161 ± 38.0 μg/mL (range 132–283) and 884 ± 82.5 μg h/mL (range 768–1106) (Table 5). On average, plasma concentrations of IPM were approximately 30-fold less than for glufosfamide. Over the glufosfamide dose range studied, IPM C_{max} and AUC increased dose-proportionally with C_{max} mean ± SD of 1.9 ± 0.3 μg/mL at 1,500 mg/m^2 and

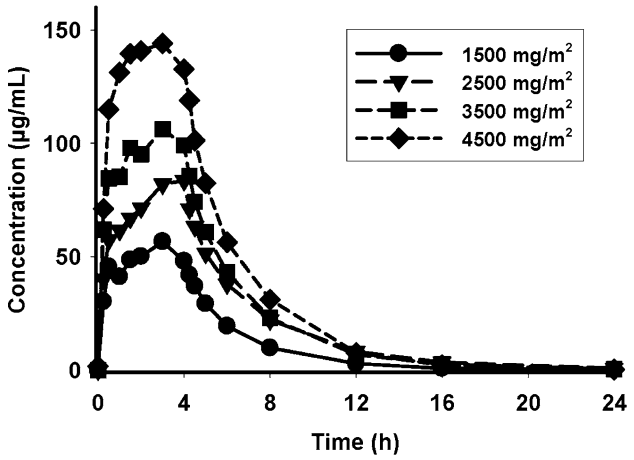

Fig. 1 Mean plasma concentrations of glufosfamide vs. time (Cycles 1 and 2 combined)

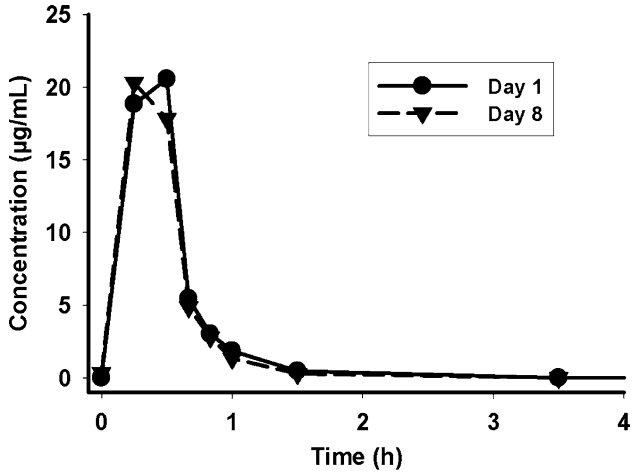

Fig. 2 Mean plasma concentrations of gemcitabine vs. time (Cycles 1 and 2 combined)

Table 5 Pharmacokinetic parameters

	C_{max} (SD) (µg/mL)	AUC (SD) (µg h/mL)
Glufosfamide[1] (n = 12)	161 (38.0)	884 (82.5)
IPM[a] (n = 12)	5.1 (1.1)	27.5 (5.38)
Gemcitabine[b] (n = 70)	24.6 (11.7)	11.5 (5.20)
dfdU[b] (n = 70)	37.1 (5.70)	232 (88)

[a] Data are for glufosfamide dose of 4,500 mg/m^2; n = number of samples at each time point

[b] Data are for all patients, regardless of glufosfamide dose

5.1 ± 1.1 µg/mL at 4,500 mg/m^2 and AUC of 11.0 ± 2.2 to 27.5 ± 5.38 µg h/mL at 1,500 and 4,500 mg/m^2, respectively.

The pharmacokinetics of gemcitabine and its major metabolite, dFdU, following a 0.5-h intravenous infusion of 1,000 mg/m^2 gemcitabine were similar on day 8 of Cycles 1 and 2 (i.e., in the absence of glufosfamide), thus, data from Cycles 1 and 2 were combined. Plasma levels of gemcitabine decreased exponentially after stopping the 30-min infusion with a mean half-life of 0.23 ± 0.08 h (Fig. 2). Mean C_{max} and AUC of gemcitabine was less than that of dFdU (Table 5). Total plasma clearance averaged 108 ± 42.1 L/h/m^2, a value exceeding hepatic plasma flow (~23 L/h/m^2) suggesting extrahepatic metabolism. The mean steady-state volume of distribution of 22.1 ± 9.34 L/m^2 suggests that gemcitabine is distributed into total body water. Plasma levels of dFdU decreased exponentially with a mean half-life of 11.2 ± 5.62 h.

Following concomitant administration of glufosfamide (day 1, Cycles 1 and 2), the pharmacokinetics of gemcitabine and dFdU were cycle-independent and glufosfamide did not affect the pharmacokinetics of gemcitabine (Fig. 2) or dFdU.

Anti-tumor activity

One unconfirmed partial response (PR) occurred in a patient with previously untreated metastatic pancreatic adenocarcinoma. Two patients had minor responses: a patient with refractory metastatic ovarian cancer had a 27% reduction in the sum of longest tumor diameters (SLD) and continued with SD after 8 cycles (32 weeks) of therapy. A patient with metastatic breast carcinoma had SD (28% decrease in SLD) that continued through 10 cycles on study. Overall 10 of 19 (52.6%) patients had SD or better after 2 cycles (8 weeks) of therapy, seven patients had continued SD at 16 weeks and three had continued SD at 24 weeks. Nine (47.4%) patients had PD categorized as their best response including one patient withdrawing with SD at Week 3 and one patient with unevaluable target lesions through Cycle 4.

Discussion

Glufosfamide has been developed as a new cytotoxic alkylating agent whose activity may be due in part to the preferential use of glucose by malignant cells. Prior phase II studies of single-agent glufosfamide showed activity in various malignancies including pancreatic, non-small cell, breast and colon cancer. Pre-clinical data suggesting synergism of glufosfamide and gemcitabine in animal models of pancreatic cancer together with interesting data from patients with pancreatic cancer, where complete and partial responses were seen with sin-

gle-agent glufosfamide, provided a rationale for testing this combined approach in a phase I study, with the goal to obtain safety, toxicity as well as preliminary activity in various tumors, particularly pancreatic cancer patients.

This phase I trial demonstrated that full dose glufosfamide may be given safely in combination with gemcitabine. The most common non-hematologic adverse events were grade 1/2 fatigue (one patient had grade 3 fatigue as DLT), nausea and vomiting. The most common hematologic adverse events were thrombocytopenia (including one DLT) and neutropenia. Thrombocytopenia was most severe by day 15 of each cycle, with recovery by day 1 of the next cycle.

Despite concerns for potential renal dysfunction with glufosfamide, CrCL in treated patients did not suffer a significant decline. The occurrence of proteinuria and occasional hypophosphatemia suggested that renal tubular dysfunction may have occurred in some patients. The lack of significant renal toxicity may be due to the small number of patients treated, the short duration of therapy in most patients and the lack of prior chemotherapy in 12 patients. Two patients had received prior cisplatin and one had received prior ifosfamide but none of these patients developed hypophosphatemia or significant reductions in CrCL.

Glufosfamide dose reductions were seldom needed. Gemcitabine dose delays and reductions were more common but it was usually possible to re-escalate the dose of gemcitabine.

Pharmacokinetic analyses showed no evidence of interaction between glufosfamide and gemcitabine. Glufosfamide's half-life of 2–3 h was similar with that seen in single-agent studies. Glufosfamide's C_{max}, AUC, Vd_{ss} and clearance in this study are comparable to those reported in the glufosfamide single-agent phase 1 study [2] where C_{max} was 407 μg/mL, AUC was between 1,129 and 1,593 μg h/mL, Vd_{ss} ranged between 17.9 and 26.8 L/m^2 and clearance ranged between 3.79 and 4.91 L/h/m^2.

Although there were no confirmed responses in this study, prolonged stable disease in two patients, one with refractory ovarian cancer and one with heavily pretreated breast cancer is indicative of activity of this drug combination in these tumor types. Gemcitabine has known antitumor activity in previously treated ovarian and breast cancer [1, 10]. In a phase 2 study of glufosfamide in metastatic breast cancer, 1 of 22 (4.5%) patients had a PR and 8 (36.4%) had SD (unpublished data). Five of the eight (62.5%) patients with pancreatic cancer had a best response of SD or better (one patient with unconfirmed PR) lasting from 3.6 to 5.7 months (4 of 6 previously untreated with chemotherapy and 1 of 2 previously treated). The median survival of the pancreatic cancer patients was similar to the overall patient population.

The safety and anti-tumor activity seen in this study provided support for an ongoing phase 2 study for patients with previously untreated, unresectable, locally advanced or metastatic pancreatic adenocarcinoma. Further clinical investigations of gemcitabine/glufosfamide combination in other tumor types including ovarian and breast cancer are warranted.

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