Phase I study of amifostine as a cytoprotector of the gemcitabine/cisplatin combination in patients with advanced solid malignancies

Missak Haigentz Jr[b], Mimi Kim[a], Joan Sorich[a], Janet Lee[a], Howard Hochster[a], Manuel Macapinlac[a], Deepu Mirchandani[a], Sanjeev Sewak[a], Anna Pavlick[a], Matthew Volm[a], Anne Hamilton[a] and Franco M. Muggia[a]

Our objective was to evaluate the role of amifostine as a cytoprotector in patients with solid tumors receiving the myelosuppressive regimen of gemcitabine/cisplatin combination. Patients with advanced solid tumors were randomized to gemcitabine–amifostine–cisplatin (GAP) or gemcitabine–cisplatin (GP) in Cycle 1 (C1) and then were crossed over to the other treatment in Cycle 2 (C2). Amifostine at 740 mg/m^2, followed by gemcitabine and cisplatin, were given for 2 consecutive weeks, every 4 weeks. Two GP combinations were studied: G 1000 mg/m^2 and P 40 mg/m^2 days 1, 8 (high dose), and G 800 mg/m^2 and P 30 mg/m^2 days 1, 8 (low dose). Forty patients were enrolled. Of the 19 patients treated with high-dose GP, 11 (nine patients GP in C1 and GAP in C2, two patients GAP in C1 and GP in C2) completed 2 cycles of therapy. Of the eight non-evaluable patients, five patients dropped out due to toxicity or refusal after treatment with amifostine in C1. Of the 21 patients treated with low-dose GP, 15 (eight patients GP in C1 and GAP in C2, seven patients GAP in C1 and GP in C2) were likewise evaluable. The incidence of grade 3 or 4 hematologic toxicities was similar for GP and GAP during the first 2 cycles of treatment, and there were no statistically significant differences in mean absolute neutrophil count, hemoglobin level and platelet levels between the cycles in each arm. We conclude that amifostine, at 740 mg/m^2, does not lead to less myelosuppression when combined with gemcitabine/cisplatin chemotherapy regimens and may possibly contribute to subjective intolerance.
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[a]Kaplan Comprehensive Cancer Center and New York University School of Medicine, New York, NY, USA and [b]Albert Einstein Comprehensive Cancer Center, Montefiore Medical Center, Bronx, NY, USA.

Correspondence to F. Muggia, New York University School of Medicine, 550 First Avenue, New York, NY 10016, USA.
Tel: +1 212 263-6485; fax: +1 212 263-8210;
e-mail: franco@muggia.com

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Introduction

Combinations of gemcitabine and cisplatin (GP) have shown activity against bladder, ovarian and lung cancers suggestive of therapeutic synergism [1–3]. Recently published phase III studies of these combinations have resulted in overall response rates of 30–41% in advanced lung cancer [4–6] and 49% in advanced bladder cancer [7]. These combinations are becoming standards of care in these malignancies.

There is, therefore, considerable interest in pursuing further study of these combinations, to optimize the dose and schedule. Since the toxicities of the two drugs overlap only minimally, combinations have generally attempted to give 1 g/m^2 of gemcitabine on 3 consecutive weeks and cisplatin at a dose of 60–100 mg/m^2 per cycle. In such regimens, myelosuppression is the dose-limiting toxicity, with hemoglobin, white cells and platelets being affected, and dose omissions are frequent. In the phase III studies mentioned above, up to 70% of patients experienced neutropenia, 30% of patients anemia and 60% of patients thrombocytopenia. Efforts to reduce the incidence of myelosuppression may make these regimens more tolerable, allowing for higher doses, perhaps resulting in improved response rates.

Amifostine, formerly known as WR-2721, is an organic thiophosphate that has been developed to selectively protect normal tissues against the toxicities of chemotherapy and radiation. Preclinical animal studies have demonstrated that the administration of amifostine protects against a variety of chemotherapy-related toxicities including cisplatin-induced nephrotoxicity [8,9], cisplatin-induced neurotoxicity [10], cyclophosphamide [11]- and bleomycin [12]-induced pulmonary toxicity, and the cytotoxicities (including cardiotoxicity) induced by doxorubicin and related chemotherapeutic agents [13,14]. Amifostine was found to decrease the toxicity of gemcitabine and cisplatin in Lewis lung tumor-bearing mice [15]. The results of clinical trials to date support a role for amifostine in protection against the nephrotoxicity, neurotoxicity and ototoxicity of cisplatin,

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and against the hematologic toxicities seen with cyclophosphamide, carboplatin and mitomycin C [16–18]. Amifostine has also been shown to reduce the incidence of a number of adverse effects including mucositis, xerostomia, dysphagia, loss of taste, leukopenia and thrombocytopenia in patients receiving radiochemotherapy for head and neck cancer [19]. These protective effects have been achieved without any evidence of a diminution of antitumor activity.

In the current study we evaluate the role of amifostine as a potential cytoprotector of the hematologic toxicities seen with a gemcitabine/cisplatin combination in a schedule where the drugs are dosed together for 2 consecutive weeks every 4 weeks. Using a randomized, two-period crossover design, we demonstrate no significant differences in the toxicities and hematologic parameters of patients treated with or without amifostine.

Patients and methods

Eligibility and randomization

Patients with histologically documented advanced solid malignancy for whom gemcitabine/cisplatin chemotherapy was appropriate were candidates for this study. Eligibility criteria also included the following: (i) age 18 years or older; (ii) ECOG performance status ≤ 2 (i.e. bedridden $< 50\%$ each day); (iii) adequate hematopoetic (absolute neutrophil count $\geq 1500/\mu$l, hemoglobin level ≥ 9.0 g/dl platelet count $\geq 100\,000/\mu$l), renal (creatinine concentration ≤ 1.5 mg/dl) and hepatic [total bilirubin concentration ≤ 1.5 mg/dl and aspartate aminotransferase (AST) $< 3\times$ upper normal limit] function; (iv) recovery from acute toxicities attributable to prior therapy (minimum of 3 weeks since last therapy); and (v) no sensory neuropathy grade > 2. All patients gave written informed consent in accordance with federal and institutional guidelines before treatment.

Eligible patients were randomized to gemcitabine–amifostine–cisplatin (GAP) or gemcitabine–cisplatin (GP) in Cycle 1 (C1) and with the other regimen in Cycle 2 (C2). This was done for each of the dosing levels.

Drug administration

This study was originally designed as a phase I toxicity followed by a standard dose-escalation study to determine the maximally tolerated doses (MTDs) of gemcitabine and cisplatin in the presence of amifostine. The plan was to start at tolerable doses of gemcitabine and cisplatin.

At the initial dose level, gemcitabine and cisplatin were administered i.v. at doses of 1000 and 40 mg/m^2, respectively. However, because of the frequently observed dropouts after the administration of amifostine-containing regimen in C1, the doses of gemcitabine and cisplatin were lowered to 800 and 30 mg/m^2, respectively. The first dose level is referred to as 'high dose' and the second level is referred to as 'low-dose'.

Throughout the study gemcitabine and cisplatin were administered for 2 consecutive weeks every 28 days. For each cycle, patients were i.v. prehydrated with 0.5 l normal saline at 250 ml/h for 2 h and premedicated with dexamethasone 10–20 mg i.v./p.o. and granisetron 0.01 mg/kg i.v. Cisplatin was administered first in 100 ml normal saline over 30–45 min. Gemcitabine was then administered in 100 ml normal saline over 30 min. Post-treatment hydration consisted of 0.5 l normal saline with 2 g magnesium sulfate at a rate of 250 ml/h for 2 h.

When used, the dose of amifostine was fixed at 740 mg/m^2 i.v. and was administered in 50 ml normal saline over 15 min immediately prior to chemotherapy. Patients were asked to void prior to amifostine administration and the patients were in a supine position during the administration.

Pretreatment and follow-up studies

Patient histories, including performance status, body surface area determinations, physical examinations and routine laboratory examinations, were obtained before treatment (baseline) and on day 1 of each cycle; laboratory examinations were also performed on day 8 of each cycle. Routine laboratory evaluations included complete blood count with differential, electrolytes, blood urea nitrogen, creatinine, calcium, phosphate, uric acid, AST, LDH, alkaline phosphatase, total bilirubin and urinalysis. Chest radiographs were performed at baseline. Radiographic tumor assessment was performed at baseline and on follow-up evaluations every 12 weeks.

Patient evaluability for this two-period crossover study consisted of completion of a minimum of two cycles of chemotherapy, with exposure to amifostine in only one cycle. Responding or stable patients continued to receive GP until disease progression.

Statistical analysis

This study was originally designed to evaluate a total of 32 evaluable patients, with 16 patients in each of two GP dosing levels, to show minimal detectable differences in granulocytes and platelet levels between GAP and GP of 800 and 55 000, respectively, with 80% power and a two-sided $\alpha = 0.5$.

For the low-dose group, absolute neutrophil count, hemoglobin and platelet levels were analyzed by fitting a mixed-effects linear model which included terms for sequence (1 = GAP/GP; 2 = GP/GAP), subject, period (baseline 1, C1, baseline 2, C2), treatment, and first- and second-order carryover effects. For the high-dose group, only the data from C1 were analyzed because of the limited number of subjects who went on to C2. Data from

the high-dose group were evaluated using an analysis of covariance model with treatment and baseline levels as the independent variables, and post-treatment levels as the dependent variable. Analyses of log-transformed data were also conducted, but are not shown because the results did not differ qualitatively from the untransformed analyses.

Results

General

Forty patients, whose pertinent characteristics are listed in Table 1, were enrolled on this study between December 1997 and April 2001, with 19 patients enrolled on the high-dose arm and 21 patients on the low-dose arm. Both arms had similar patient age, gender distribution, ECOG performance status and incidence of prior therapies, and a varied distribution of representative malignancies.

Table 2 presents the evaluability data of the patients and the reasons for dropout. Of the 19 patients on the initial, high-dose study arm, only 11 patients were able to complete two cycles of therapy and were therefore evaluable. Of the remaining non-evaluable eight patients, five patients did not receive C2 due to toxicity or refusal; all five randomized patients received amifostine in C1. This difference was significant ($p = 0.03$). Only one patient did not receive C2 due to disease progression. Because of the apparent subjective intolerance to amifostine seen at these doses of gemcitabine and cisplatin, patient accrual was terminated at the high-dose level and accrual to the low-dose arm was initiated.

Of the 21 patients enrolled on the low-dose study arm, 15 patients were able to complete two cycles and were therefore evaluable. Only one patient dropped out due to refusal, and that patient refused participation on the study just after randomization and was not treated. No patients dropped out due to intolerable toxicity. Five patients on this arm, however, experienced disease progression prior to completing two cycles of therapy.

Table 1 Characteristics of patients enrolled on high-dose and low-dose gemcitabine/cisplatin regimens.

	High dose	Low dose
No. patients	19	21
Median age	63 (range 38–87)	56 (range 36–77)
Sex		
males	9	10
females	10	11
ECOG performance status (*n*)		
0	1	5
1	15	14
2	3	2
Median no. prior chemotherapy treatments	2 (range 0–9)	1 (range 0–4)
Prior radiation (*n*)	6	6
Tumor types		
Lung	9	5
Ovarian	2	3
Uterine cervix	1	1
Gastric	3	7
Esophageal	1	0
Colorectal	0	2
Head and neck	0	1
Thyroid	0	1
Unknown primary	3	1

Therapeutic results

Among the randomized patients with radiographic follow-up performed during therapy, the best response to GP combination was determined. Of 12 patients treated on the high-dose GP arm, one patient had a partial response to therapy, six had stable disease and five had evidence of disease progression. Of 17 patients treated on the low-dose arm, five had stable disease; the remaining 12 patients had disease progression. The average number of cycles of GP administered was 3.0 for both the high-dose and low-dose arms.

Hematologic toxicities

Among all of the evaluable patients, the incidence of observed grade 3 and 4 hematologic toxicities during the two cycles for the high- and low-dose study arms is listed in Table 3. As expected, far more grade 3 and 4 hematologic toxicities were observed in the high-dose arm compared to the low-dose arm. No grade 4 hematologic toxicities occurred in the low-dose arm and the only two observed bleeding events (one retinal and one gastrointestinal bleed) were associated with significant thrombocytopenia that occurred in the high-dose arm. Among the evaluable high-dose patients, no

Table 2 Evaluability of randomized patients according to the sequence of therapy in the presence and absence of amifostine

	High dose		Low dose	
	C1 GAP/C2 GP	C1 GP/C2 GAP	C1 GAP/C2 GP	C1 GP/C2 GAP
No. randomized patients	9	10	11	10
No. completing crossover	2 ($p=0.03$[a])	9	7 ($p=0.64$[a])	8
Not evaluable	7	1	4	2
Reasons for not completing crossover				
progression	0	1	3	2
toxicity	1	0	0	0
refusal	4	0	1	0
other	2	0	0	0

[a]Fisher's exact test.

significant inter-cycle difference was observed in the incidence of grade 3 or 4 toxicities.

Table 4 presents the mean baseline and nadir absolute neutrophil count, platelet level, and hemoglobin levels for the patients in each cycle by crossover sequence in the high-dose (Table 4A) and low-dose (Table 4B) study arms. Again, no significant treatment differences were observed between the GAP and GP regimens for each of the variables. As there was no evidence of carry-over effects, additional models were fit excluding these terms, but treatment differences remained non-significant. Among patients in the low-dose arm, the mean baseline levels of absolute neutrophil count and hemoglobin were similar between cycles. However, the baseline platelet levels of patients on the low-dose arm at C2 were greater than pretreatment levels, regardless of prior amifostine treatment status.

Non-hematologic toxicities

Because of the high dropout rates seen in the high-dose arm, particularly those associated with amifostine given in the first cycle, analysis of the non-hematologic toxicity of GAP and GP was done to include all randomized and treated patients during the first cycle of therapy only. Table 5 lists the incidence of Grade 1–4 non-hematologic toxicities observed during the first cycle of therapy. Among the 19 patients treated in the high-dose arm, the only observed grade 3 non-hematologic toxicity was anorexia in one patient. Most observed toxicities were grade 1 and 2 nausea, vomiting, anorexia, dizziness and fatigue. Only one grade 1 nephrotoxicity was observed in the high-dose arm and that one occurred in a patient who did not receive amifostine in C1. No significant (grade 3 or 4) episodes of hypotension were observed the amifostine-treated groups. Amifostine did not appear to decrease any of the observed toxicities; rather there appears to be a trend towards increased grade 1 and 2 toxicities in the amifostine-exposed groups.

Table 3 Incidence of grade 3/grade 4 hematologic toxicities among evaluable patients.

	C1 GP	C2 GAP	C1 GAP	C2 GP
High dose	*N*=9 patients		*N*=2 patients	
neutropenia	2/1	2/0	1/0	0/0
anemia	0/0	1/0	0/0	0/0
thrombocytopenia	1/2[a]	4[b]/1	0/0	0/0
Low dose	*N*=8 patients		*N*=7 patients	
neutropenia	2/0	0/0	0/0	0/0
anemia	0/0	0/0	0/0	1/0
thrombocytopenia	2/0	0/0	2/0	0/0

[a]Includes one patient with grade 2 retinal bleed.
[b]Includes one patient with grade 3 gastrointestinal bleed.

Discussion

Myelosuppression is a frequent dose-limiting toxicity of gemcitabine/cisplatin combination regimens, and its amelioration is appealing in terms of improved patient tolerance and the potential for increased dose-intensity and perhaps response. An improvement in the tolerability and therapeutic index for these agents is leading to a focus on scheduling [20–24]. Alternatively, the use of growth factors to prevent hematologic toxicity with gemcitabine/cisplatin regimens has not been studied because of cost, inconvenience and requirement of a separate growth factor to support each component of the bone marrow.

The cytoprotective benefits of amifostine, along with its broad mechanisms of action in protecting non-malignant

Table 4 Average baseline and nadir platelet, absolute neutrophil count (ANC) and hemoglobin (Hb) levels for each cycle of therapy

(A) High dose (C1 data only)	Baseline for C1	C1 nadir	Difference	*p* value
Mean platelet levels/μl (SD)				
GAP	271.56 (80.48)	88.00 (75.51)	−183.56	0.87
GP	256.70 (90.98)	85.70 (56.90)	−171	
Mean ANC levels/μl (SD)				
GAP	4574.89 (1648.26)	1782.78 (2094.24)	−2972.11	0.96
GP	4304.20 (2280.29)	1583.60 (1091.78)	−2720.6	
Mean Hb levels g/dl (SD)				
GAP	12.11 (1.13)	9.42 (2.38)	−2.69	0.15
GP	11.15 (1.95)	9.98 (1.43)	−1.17	
(B) Low dose	**Baseline for C1**	**C1 nadir**	**Baseline for C2**	**C2 nadir**
Mean platelet levels/μl (SD)				
p value, treatment=0.80				
GAP/GP	275.14 (111.84)	119.43 (65.13)	476.29 (105.37)	184.71 (73.52)
GP/GAP	271.88 (68.58)	99.50 (55.66)	538.25 (170.01)	116.25 (48.08)
Mean ANC levels/μl (SD)				
p value, treatment=0.46				
GAP/GP	7270.86 (4443.68)	2111.14 (1219.98)	7241.29 (4787.22)	4209.71 (3048.01)
GP/GAP	5828.13 (2125.39)	1766.00 (1123.81)	4718.00 (2143.37)	2986.00 (1976.07)
Mean Hb levels g/dl (SD)				
p value, treatment=0.28				
GAP/GP	12.49 (2.26)	11.36 (2.49)	12.19 (1.92)	10.87 (2.62)
GP/GAP	11.59 (1.19)	9.81 (0.80)	10.46 (0.85)	9.61 (0.88)

(A) High-dose arm patients. Due to the large number of dropouts following the first cycle, only C1 data is presented.
(B) Low-dose arm patients. C1 and C2 data are presented.

Table 5 Incidence of grade 1/2/3/4 non-hematologic toxicities of all randomized patients treated during C1

	High dose		Low dose	
	GAP (*N*=9 patients)	GP (*N*=10 patients)	GAP (*N*=10 patients)	GP (*N*=10 patients)
Nausea	5/0/0/0	4/1/0/0	30/0/0	1/0/1/0
Vomiting	4/0/0/0	2/0/0/0	2/0/0/0	2/1/0/0
Anorexia	1/1/0/0	2/0/0/0	1/0/0/0	2/0/0/0
Hypotension	0/2/0/0	0/1/0/0	0/0/0/0	0/0/0/0
Dizziness/ headache	1/0/0/0	0/0/0/0	2/1/0/0	0/0/0/0
Fatigue	2/0/0/0	1/2/0/0	1/1/0/0	0/1/0/0
Renal insufficiency	0/0/0/0	1/0/0/0	0/0/0/0	0/0/0/0

cells, led to testing amifostine as a hematologic cytoprotector in gemcitabine/cisplatin combinations. Amifostine is currently approved by the Food and Drug Administration for the prevention of cisplatin-induced nephrotoxicity and ototoxicity, and some hematopoetic cytoprotection for cisplatin has also been suggested [25]. No published studies to date have demonstrated protection from gemcitabine-induced toxicities.

This study used a relatively novel administration schedule of the drugs in which the chemotherapeutic agents were dosed for 2 consecutive weeks. There has been some evidence that gemcitabine may interfere with the repair of cisplatin–DNA adducts. Concurrent cisplatin may also lead to increased incorporation of gemcitabine into DNA [26,27]. This dosing regimen has shown clinical activity against ovarian cancer in the presence of amifostine [28] and this concept has recently been utilized in a phase II regimen for non-small cell lung cancer [20]. Although the current study did not evaluate the efficacy of this regimen, there were clearly more patients who had disease progression during the first two cycles of therapy in the low-dose group than the high-dose group, suggesting that the lower dose regimen, although tolerable in terms of side effect profile, was not efficacious. Further studies are needed to demonstrate the optimal dose and schedule in gemcitabine/cisplatin regimens.

The intent of this study was to demonstrate an improved hematologic toxicity profile of a gemcitabine/cisplatin combination in the presence of amifostine and to subsequently increase the dose of the agents in a standard phase I dose escalation study to determine a new MTD for use in phase II trials. A randomized two-period crossover study was selected to evaluate the toxicity of the regimen with amifostine, requiring a smaller number of enrolled patients than traditional parallel studies, with each patient serving as his or her own control. The large number of dropouts, particularly in the high-dose arm, was unexpected, complicated the analysis and led to a relative dose de-escalation to complete the study. Most of the dropouts occurred in the high-dose arm following C1 with amifostine and were due to toxicity or patient refusal to continue protocol therapy. Since no significant toxicities were observed other than a trend toward increased grade 1–2 non-hematologic toxicities in the presence of amifostine, the dropouts were likely due to subjective intolerance to amifostine in this setting. This observation could be interpreted as increased toxicity or subjective intolerance to amifostine in combination with gemcitabine/cisplatin regimens.

A rather surprising observation was that although the mean baseline absolute neutrophil count and hemoglobin levels of the patients in the low-dose arm were similar between the two cycles, the mean platelet counts at baseline for C2 were greater than pretreatment levels (Table 4B). This observed rebound thrombocytosis, not previously described for gemcitabine/cisplatin regimens, occurred whether amifostine was given or not in C1. The opportunity to observe this phenomenon may be related to the modest dose of cisplatin and the 4-week dosing interval.

Amifostine, at a dose of 740 mg/m^2 given just prior to the chemotherapy, was not shown to improve the hematologic profile of this gemcitabine/cisplatin regimen. Although there has been some controversy regarding the proper dosing of amifostine, pharmacokinetic studies suggest that the 740 mg/m^2 dose provides its maximal availability and, therefore, maximal cytoprotection, due to saturation of alkaline phosphatase in normal cells [29]. Other studies have suggested increased cytoprotection when it is dosed both prior to and following chemotherapy [25]. Such a regimen in combination with gemcitabine and cisplatin has not been studied, but is likely to result in increased toxicity and intolerance from amifostine. We conclude that amifostine should not be recommended as a hematologic cytoprotector in gemcitabine/cisplatin regimens. Studies employing other cytoprotective agents and prophylactic growth factor administration should be considered in attempts to improve the patient tolerance and therapeutic index of this effective chemotherapeutic combination.

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