Pooled efficacy analysis from a phase I–II study of biweekly irinotecan in combination with gemcitabine, 5-fluorouracil, leucovorin and cisplatin in patients with metastatic pancreatic cancer

Anupama Goel[a], Michael L. Grossbard[a,b], Stephen Malamud[b], Peter Homel[c], Margaret Dietrich[b], Teresa Rodriguez[a], Takhir Mirzoyev[a] and Peter Kozuch[a]

Development of treatments to improve the outcomes achieved with single-agent gemcitabine therapy for metastatic pancreatic cancer remains a research priority. G-FLIP (gemcitabine, 5-fluorouracil, leucovorin and cisplatin) is a four-drug regimen designed to maximize sequence-dependent synergy, while attempting to minimize toxicity among the four drugs. The dose-limiting toxicities and maximum tolerated dose of irinotecan as part of the G-FLIP regimen have been published. For phase II testing, G-FLIP consisted of sequential gemcitabine 500 mg/m^2 at a fixed rate of 10 mg/m^2/min, irinotecan 120 mg/m^2, bolus 5-fluorouracil 400 mg/m^2 and leucovorin 300 mg, followed by a 24-h 5-fluorouracil infusion of 1500 mg/m^2 on day 1 and cisplatin 35 mg/m^2 on day 2. Cycles were repeated every 14 days. Thirty-three patients with metastatic pancreatic cancer (22 men and 11 women) were treated and 31 were evaluable. Median patient age was 63 years (range 44–78 years) and median Karnofsky performance status score was 70–80. Estimated median time to disease progression was 171 days (6.1 months) and Kaplan–Meir-estimated median overall survival was 229 days (8.1 months). Twelve- and 18-month survivals were 33 and 21%, respectively. As per Response Evaluation Criteria in Solid Tumors criteria, 13 patients had stable disease, seven (22%) attained a partial response, and 10 (32%) had disease progression. One patient attained a complete response and two were not evaluable (one withdrew consent and one died suddenly, each after cycle 1). Treatment generally was well tolerated. Grade 3–4 toxicities/patient were thrombocytopenia (3.1%), leukopenia (15%), neutropenia (21%), neutropenic fever (3%), fatigue (18%) and thrombosis (12.5%). Common grade 1–2 toxicities per patient included nausea/vomiting (69%), diarrhea (45%), constipation (21%) and fatigue (39%). In conclusion, G-FLIP is a feasible outpatient regimen with acceptable toxicity for metastatic pancreatic cancer patients. Disease control rate (stable disease rate plus partial or complete responses) and 1-year survival outcomes are encouraging. *Anti-Cancer Drugs* 18:263–271 © 2007 Lippincott Williams & Wilkins.

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[a]Department of Medicine, Division of Hematology/Oncology, St Luke's-Roosevelt Hospital Center, [b]Department of Medicine, Division of Hematology/Oncology and [c]Department of Pain Medicine and Palliative Care, Beth Israel Medical Center, New York, New York, USA.

Correspondence to Dr Peter Kozuch, MD, 10 Union Square East, Suite 4C-02, New York, NY 10003, USA.
Tel: +1 212 523 6769; fax: +1 212 523 2004;
e-mail: pkozuch@chpnet.org

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Introduction

Gemcitabine is currently the standard first-line palliative therapy for patients with advanced or metastatic pancreatic cancer. Unfortunately, clinical benefit response (CBR) is achieved in only 23% of patients, median survival is 5–6 months and 1-year survival is 20% or less [1]. Many different cytotoxic agents have been evaluated in combination with gemcitabine, but with the exception of gemcitabine and capecitabine no doublet has demonstrated survival benefit beyond gemcitabine alone [2].

The G-FLIP regimen [gemcitabine, 5-fluorouracil (5-FU), cisplatin and irinotecan] was designed to maximize sequence-dependent additive or synergistic interactions while attempting to minimize sequence-dependent toxic effects among the four drugs. The schedule and sequence were based on preclinical as well as phase I and phase II trials of the chemotherapeutic agents used as doublets (Fig. 1) [3–17]. A retrospective analysis of 34 heavily pretreated metastatic pancreatic cancer patients treated with the G-FLIP regimen reported a partial response (PR) rate of 24% and a median survival of 10.3 months [18]. The favorable response and survival outcomes demonstrated by the retrospective analysis encouraged prospective phase I–II evaluation of a regimen modified to enable outpatient administration and with drug dosing/scheduling based on the median dose intensity tolerated in the retrospective analysis. In the current trial, administration of 5-FU was modified to a continuous 24-h infusion via ambulatory pump on day 1 for

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Fig. 1

I→5-FU	Additive efficacy, less diarrhea and neutropenia [13, 14]
G→P	Gemcitabine 24 h then cisplatin lowers cisplatin plasma levels, increase platinum–DNA adducts lessens leucopenia [15]
F→P	Maximizes synergistic activity *in vitro* [16]
I→P	No observed sequence-dependent effects [5]
G→I	No sequence-related synergy, toxicity or pharmacokinetic interaction [18]
G→F	No published data on sequence effects

Treatment sequence rationale administration of 5-FU after irinotecan is associated with less side-effects, mainly diarrhea and neutropenia. This is in part explained by pharmacokinetic analysis suggesting a reduced formation and area under curve of SN-38. Cisplatin exerts its cytotoxic effects by the formation of DNA adducts and these can be increased by administration of cisplatin 24 h after gemcitabine infusion. I, irinotecan; 5-FU, 5-fluorouracil; G, gemcitabine; P, cisplatin.

outpatient treatment. The phase I study established the maximum tolerated dose of irinotecan as 120 mg/m^2 in combination with fixed doses of other three drugs as described in the Patients and methods section [19].

Here we are reporting the final results of antitumor activity measured as disease control rate [DCR; defined as the sum of disease stabilization rate, PR and complete response (CR) rates, all as per Response Evaluation Criteria in Solid Tumors (RECIST) criteria], time to tumor progression and carbohydrate antigen 19-9 (CA 19-9) response in 33 patients with metastatic pancreatic cancer. Owing to slower than expected eligible patient referrals, patients with metastatic pancreatic cancer treated on either phase I or phase II trial were pooled for this final efficacy analysis. That is, outcomes of the 12 patients with metastatic pancreatic cancer treated in the phase I trial were combined with outcomes of the 21 patients treated in the phase II trial for this analysis.

Patients and Methods

Patient eligibility

The protocol was approved by our local institutional review board. A signed informed consent was obtained from all patients before study entry. Patients were eligible for this study if they were 18 years of age or older and had histologically or cytologically confirmed pancreatic adenocarcinoma. Patients also were required to have metastatic pancreatic cancer, a Karnofsky performance status (KPS) score of ≥ 60, absolute granulocyte count $\geq 1500/mm^3$, platelet count $\geq 100\,000/mm^3$, bilirubin ≤ 2.0 mg/dl and a creatinine of ≤ 1.5 mg/dl. In addition, all patients had measurable or evaluable metastatic disease as defined by the RECIST criteria. Important exclusion criteria were brain metastasis or leptomeningeal disease, progressive sensory neuropathy or hearing loss, tinnitus, life expectancy less than 12 weeks, uncontrolled medical conditions such as diabetes or hypertension and previous irinotecan or topoisomerase I inhibitor treatment. Previous adjuvant radiation or chemoradiation with 5-FU or gemcitabine was permissible.

Study design and treatment

The G-FLIP treatment scheme is outlined in Fig. 2. Therapy was administered in an outpatient setting every 2 weeks (equals one cycle). Antiemetic choice was as per the discretion of each treating clinician, but 5-HT$_3$ receptor antagonists and dexamethasone were recommended. During the first two cycles of the phase I portion of this trial, the use of hematopoietic colony-stimulating factors was restricted to indications set forth by the American Society of Clinical Oncology [20].

Efficacy and safety evaluation

Standard efficacy endpoints of disease stabilization and objective tumor response rate, time to progression (TTP), survival time, and CBR were assessed. Baseline tumor evaluations were performed within 14 days before the start of treatment. Tumor responses were evaluated every 8 weeks by objective, two-dimensional measurements of evaluable tumors along the longest diameter according to RECIST criteria, employing imaging techniques such as computed tomography scans or magnetic resonance imaging. A CR was defined as the disappearance of all measurable and evaluable disease for at least 4 weeks without the appearance of new lesions. A PR was defined as at least a 30% decrease in the sum of the longest diameter of all measurable lesions from baseline without the appearance of new lesions. Progressive disease was defined as at least a 20% increase in the sum of the longest diameter of the measurable lesions or the appearance of new lesions. Stable disease was defined as insufficient decrease in tumor to qualify for a PR or insufficient increase in size to qualify for progressive disease. A minimum of two courses of treatment were required for radiological disease evaluation. All patients who received any therapy with G-FLIP were evaluable for toxicity. Patients who attained a CR could continue chemotherapy for 6 months beyond CR. Patients attaining a PR were allowed to continue chemotherapy until disease progression. Patients were withdrawn from therapy in case of disease progression, patient's refusal, physician's preference or development of any toxicity that precluded further therapy.

Fig. 2

Day 1	Day 2
Gemcitabine 500 mg/m^2 (in 100 cm^3 of physiological saline at 10 mg/m^2/min)	Cisplatin 35 mg/m^2 in 50 cm^3 physiological saline over 45 min
Irinotecan 120 mg/m^2 (in 500 cm^3 D5W over 90 min)	
Leucovorin 300 mg (in 50 cm^3 of physiological saline over 10 min)	
5-FU 400 mg/m^2 (in 50 cm^3 normal saline over 10 min)	
5-FU 1500 mg/m^2 via pump over 24 h	

1. *Pre-hydration* – mannitol 12.5 g in 500 cm^3 of D5½NS over 30–60 min followed immediately by post-hydration.
2. Cisplatin infusion was allowed to start after first mannitol infusion if urine output was at least 100 cm^3/h. Lasix 10–20 mg could be administered during or immediately after the cisplatin infusion.
3. *Post-hydration* – 25 g of mannitol in 1000 cm^3 of ½ physiological saline with 30 mEq KCl and 2 g of magnesium sulfate over 2–4 h an additional mannitol 25 g in 1l of ½ normal saline with 30 mEq KCl and 2 g of magnesium sulfate over 2–4 h.
4. Cycles to repeat every 2 weeks.
5. All drugs were infused intravenously.

Gemcitabine, 5-fluorouracil (5-FU)/leucovorin, irinotecan and cisplatin (G-FLIP).

CBR, as defined by Burris *et al.* [1] was based on changes in patient's pain, performance status, and weight. A patient was considered to be a clinical benefit responder if either of the primary measures of pain or KPS was classified as positive without the other being negative. Pain response was defined as improvement in pain score by 50% from baseline lasting for more than 4 weeks or decrease in analgesic use by 50% from baseline and sustained for 4 weeks. Improvement in KPS score by 20 points that was sustained for 4 weeks was qualified as a positive clinical response. If either pain or performance status worsened, the patient was classified as a clinical benefit nonresponder. If pain and performance status were both stable, then the secondary measure of weight change was used to determine clinical benefit. Positive weight change was defined as an increase by 7% and lasting for 4 weeks. If the patient, however, developed third space fluid or required parenteral nutrition, they were considered nonpositive for weight change. Any other change or weight stabilization was defined as nonpositive.

Safety evaluations consisted of weekly assessment of adverse events, complete blood counts and basic metabolic chemistries. Toxicity was graded using the National Cancer Institute Common Toxicity Grading Criteria (version 2.0). Drug-specific dose adjustments were made prior to subsequent cycles in case of toxicity. Chemotherapy was held for granulocyte count $< 1000/mm^3$, platelets $< 100\,000/mm^3$ or neutropenic fever. The 24-h 5-FU infusion dose was decreased by 25% for grade 3/4 stomatitis and grade 2 or greater hand–foot syndrome. The 5-FU bolus was reduced by 50% if the early neutropenic nadir, defined as fall in absolute neutrophil count on or before day 8, was $< 1000/mm^3$ and 5-FU was deleted if it was less then $500/mm^3$. Cisplatin dose was decreased by 25% for neutropenic fever, platelet count $\leq 100\,000/mm^3$ at day 14, platelet count nadir $\leq 50\,000$ or for grade 1–2 persistent neuropathy. Cisplatin dose was reduced to 20 mg/m^2 and administration changed to continuous 24-h infusion if serum creatinine increased to 1.5–3.0 mg/dl. Irinotecan-associated acute or delayed diarrhea was treated symptomatically with atropine or loperamide, respectively, and irinotecan dose was reduced by 25% for grade 3–4 diarrhea.

Statistical methods

The phase I portion of this trial used the 'modified Fibonacci' 3 + 3 dose escalation design [19]. A Simon two-stage phase II design was used to determine whether there was sufficient activity to warrant complete enrollment. The primary outcome of this efficacy analysis was DCR defined as the sum of CR, or PR, and disease

stabilization persisting for at least 8 weeks. Secondary outcomes were CBR and survival. Cessation of the trial was based entirely on the primary outcome.

A 10% DCR was assumed as the baseline rate of response, whereas a 30% DCR was considered the desired rate to detect. Using a solution that minimized the number of patients needed for the first stage, if two or fewer of the first 15 evaluable patients experienced disease control, enrollment was to be terminated. If three or more patients of the first 15 evaluable patients attained disease control, enrollment was to continue to the full sample of 31 patients. If six or fewer patients of 31 attained disease control, then the conclusion would be that the treatment was not effective. If seven or more of 31 patients (23%) attained disease control, then that would be considered as evidence supporting for further research. This design had a power of 80% to detect a 30% DCR with $\alpha = 0.025$.

For CBR, the assumed base rate was 5 versus 24% as the desired rate to detect. It was assumed that some patients might not comply with the clinical benefit questions. If none of first evaluable nine patients demonstrated evidence of CBR, then no further data on clinical benefit would be collected. If at least one patient out of the first nine showed clinical benefit and if the rule for continuing to stage 2 was met, then CBR data from an additional 15 evaluable patients would be collected for a total sample of 23 patients.

If three or fewer of 23 patients showed evidence of CBR then the conclusion would be that there was no increased CBR associated with G-FLIP. If four or more of 23 patients (17%) showed evidence of CBR then the conclusion was that the treatment is effective in increasing rates of clinical benefit. This sample had a power of 80% to detect a 24% CBR (versus 5%) with $\alpha = 0.025$. It allows for a 26% noncompliance rate (eight patients) out of the overall sample of 31 patients. A Bonferroni adjusted α of 0.025 was used to adjust for the fact that two outcomes were being tested with a two-stage design. The Kaplan–Meier estimate was used for comparison of survival times between groups, whereas Cox proportional hazards regression was used for continuous predictors. All analyses were performed using the statistical package SPSS 13.0.1 (SPSS, Chicago, Illinois, USA).

Results

Patient characteristics

A total of 33 patients were enrolled between March 2002 and April 2005 (Table 1). Twenty-two men and 11 women with a median age of 63 years (range 44–78 years) and a median KPS of 70–80 were enrolled. Thirty-one patients were evaluable for response. Two patients were unevaluable: one patient died suddenly after cycle 1 likely because of an unconfirmed pulmonary embolism and another patient withdrew consent after cycle 1.

Table 1 Baseline patient characteristics ($n = 33$)

Characteristic	No.	%
Age (years)		
Median	63	
Range	44–78	
Sex		
Male	22	66.6
Female	11	33.3
Performance status (Karnofsky)		
90–100	16	48
70–80	11	33
60	2	6
Unknown	4	13
Prior treatment (G + docetaxel, G + erlotinib)	1 each	6
Elevated CA19-9	24	72

G, gemcitabine.
All patients had stage IVb disease, either confirmed histologically or based on radiographic findings.

Response and survival outcomes are summarized in Table 2. DCR was observed in 21 patients (68%): one patient had a CR, seven patients attained PR and stable disease of at least 8 weeks was seen in 13 patients. In addition, CBR was observed in 52% (12 out of 23 patients evaluable for CBR). The Kaplan–Meier-estimated median TTP for the full sample was 171 days (95% confidence interval: 95–247) whereas Kaplan–Meier-estimated median overall survival was 229 days (95% confidence interval: 132–326) (Figs 3 and 4). Twelve- and 18-month survivals were 33 and 21%, respectively. As summarized in Table 3, CBR was not significantly associated with either TTP (206 versus 156 days, $P = 0.28$) or overall survival (277 versus 251 days, $P = 0.36$). CA 19-9 response was available in 15 patients and serum CA 19-9 fell by more than 50% in 11 patients. Treated as a continuous predictor, change in CA 19-9 showed a trend toward being associated with TTP ($P = 0.10$) and was significantly related to survival ($P = 0.048$). Patients with greater than 50% reduction in CA 19-9 had a median TTP of 277 days and a median overall survival of 536 days versus 118 and 165 days, respectively, for patients with 50% or less CA 19-9 reduction.

Of the 12 patients from the phase I study pooled for this analysis, six received an irinotecan dose less than 120 mg/m^2. Disease control rate for these patients was 100% and the median overall survival was 228 days, similar to the median OSS of the entire study cohort.

A total of 203 cycles were administered to 33 patients, with patients receiving a median number of seven cycles (range 1–16 cycles). Thirty-six cycles (17%) were delayed, 28 cycles for 1 week and eight cycles for 2 weeks. Most delays were due to thrombocytopenia

Table 2 G-FLIP treatment results

Response	Patients (%) $n=31$, evaluable patients
Disease Control rate (SD/PR/CR)	21 (68)
Stable disease (SD)	13 (42)
Partial response (PR)	7 (23)
Complete response (CR)	1 (3)
Progressive disease (PD)	10 (32)
Time to tumor progression (TTP)	171 days (6.1 months)
Median overall survival	229 days (8.1 months)

Table 3 TTP and OSS based on CBR

	N	DFS (days)	OSS (days)
Positive CBR	12	206	277
Negative CBR	11	156	251
P value		0.28	0.36

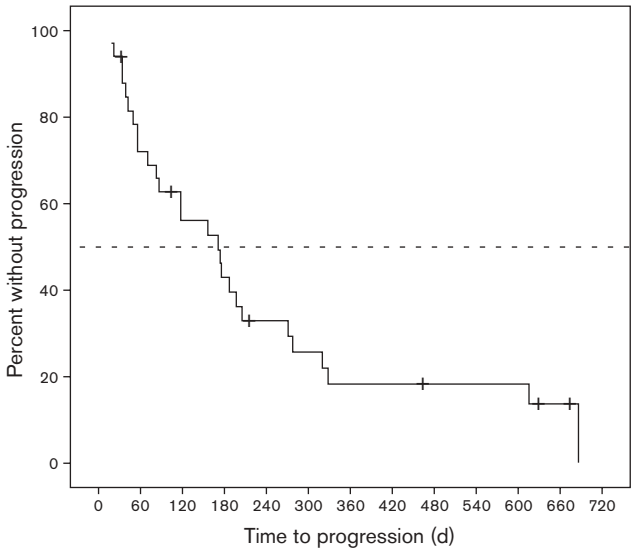
CBR, clinical benefit ratio; DSS, disease-free survival; OSS, overall survival.

Table 4 Grade 3 and 4 toxicities of G-FLIP as compared with single-agent gemcitabine and GEMOX

Toxicity	G-FLIP (%)	Gemcitabine (%) [2]	Gemcitabine and oxaliplatin (%) [27]
Hematological toxicity			
Neutropenia	21	25	20.4
Leukopenia	15	9	NA
Anemia	6	9	6.4
Thrombocytopenia	3	9	14
Nonhematological toxicity			
Nausea/vomiting	9	12	10/8.9
Diarrhea	0	1.6	5.7
Fatigue	18	NA	NA
Neutropenic fever	3	NA	1.3
Alopecia	0	0	NA

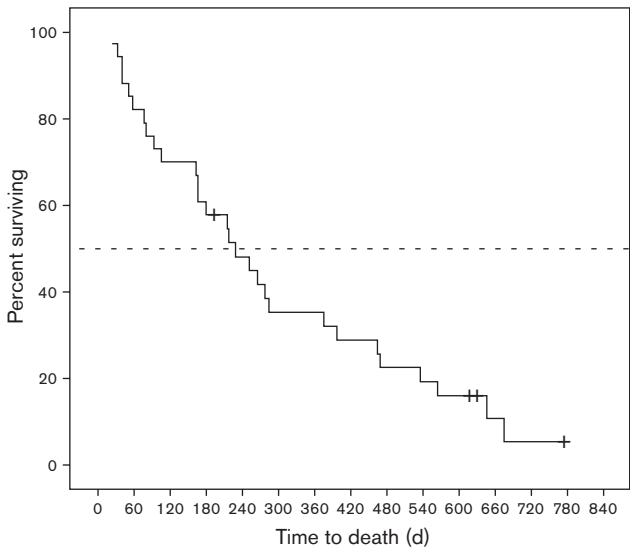
NA, not available.

Fig. 3



Kaplan–Meier estimate of median time to tumor progression.

Fig. 4



Kaplan–Meier estimate of median time to overall survival.

(3.9%), neutropenia (2%), fatigue (1.5%), diarrhea (1%), nausea/vomiting (1%) and patient's request (3.4%). A 2-week delay for reversible nephrotoxicity occurred in one patient. As specified by the protocol, dose reduction for one medication was required in five patients. Four patients required cisplatin dose reduction; one each for nausea and vomiting, thrombocytopenia (cycle 8), ototoxicity (cycle 8), and in one patient dose was decreased to 20 mg/m^2 for transient increase in creatinine. In one patient both cisplatin and irinotecan doses were reduced for nausea and vomiting in cycle 4.

Toxicity

The G-FLIP regimen generally was well tolerated and was easily administered in the outpatient setting. The incidence of significant hematological and nonhematological toxicities was low (Table 4). The 12.5% rate of grade 3–4 thrombosis is consistent with the expected rate of thromboses in pancreatic cancer patients. Common grade 1–2 toxicities per patient were nausea/vomiting (69%), diarrhea (45%), constipation (21%) and fatigue (39%).

Discussion

The development of effective chemotherapy in patients with locally advanced or metastatic pancreatic cancer remains a challenge. Since 1997, gemcitabine has been the standard treatment option in this patient population. The Food and Drug Administration has recently approved erlotinib in combination with gemcitabine for the treatment of pancreatic cancer on the basis of a randomized phase III placebo controlled trial that demonstrated a statistically significant prolongation of

Table 5 Clinical trials with gemcitabine alone and gemcitabine combinations in patients with advanced or metastatic pancreatic cancer

Study	Evaluable patients	Treatment	Estimated 1-year survival (%)	Median survival (months)	*P*-value
Burris [1]	126	Gemcitabine	18	5.6	0.0025
		5-FU	2	4.4	
Berlin *et al.* [22]	322	Gemcitabine	Less than 20	5.4	0.09
		Gemcitabine/5-FU	Less than 20	6.7	
Rocha Lima *et al.* [23]	360	Gemcitabine	20	6.6	0.789
		Gemcitabine/Irinotecan	20	6.3	
O'Riley *et al.* [24]	349	Gemcitabine		6.2	0.52
		Gemcitabine/Exatecan		6.7	
Oettle *et al.* [25]	365	Gemcitabine	20.1	6.3	0.848
		Gemcitabine/Pemetrexed	21.4	6.2	
Louvet *et al.* [26]	313	Gemcitabine	8-month; 45	7.1	0.13
		Gemcitabine/Oxaliplatin	8-month; 56	9.0	
Cunningham *et al.* [2]	533	Gemcitabine	19	6.0	0.026
		Gemcitabine plus Capecitabine	26	7.4	
Herrmann *et al.* [27]	319	Gemcitabine		7.3	0.314
		Gemcitabine/Capecitabine		8.4	
Colucci *et al.* [28]	107	Gemcitabine		5 (20 weeks)	0.43
		Gemcitabine/Cisplatin		7.5 (30 weeks)	
Riess *et al.* [29]	466	Gemcitabine	22	6.2	0.68
		Gemcitabine/continuous infusion 5-FU/FA	21	5.85	
Moore [21]	569	Gemcitabine	17	6.4	0.025
		Gemcitabine plus Erlotinib	24	5.9	

5-FU, 5-fluorouracil; FA, folinic acid.

median overall survival (6.37 versus 5.91 months, $P = 0.025$) favoring this novel doublet [21]. One-year survival was 24% with gemcitabine/erlotinib versus 17% with gemcitabine/placebo. No difference was found in overall response rate between gemcitabine/erlotinib and gemcitabine/placebo, 9 versus 8%, respectively.

Many different cytotoxic agents have been evaluated in combination with gemcitabine. With the exception of capecitabine (Xeloda) and gemcitabine, none of the two-drug combinations have significantly improved survival (Table 5) [1,2,22–29]. In a phase III randomized study, reported only in abstract form, gemcitabine and capecitabine were associated with an improved response rate (14 versus 7%, $P = 0.0008$) as well as improved overall survival (7.4 versus 6 months, $P = 0.026$) compared with gemcitabine alone [2].

While phase III trials evaluating gemcitabine versus gemcitabine and other cytotoxic chemotherapies have been disappointing, recent meta-analyses suggest a benefit from combination chemotherapy. One meta-analysis of trials in patients with inoperable pancreatic cancer showed a significant improvement for gemcitabine-based combinations with respect to 6-month survival rate [risk difference (RD) of 4%, $P = 0.02$], objective response rate (RD 5%, $P = 0.01$) and 6-month progression-free survival (RD 10%, $P < 0.0001$) [30]. Only marginal improvement, however, was observed for gemcitabine-based combinations regarding 1-year survival rate (RD 3%, $P = 0.05$) and clinical benefit rate (RD 7%, $P = 0.06$). A second similar meta-analysis showed an overall survival benefit with gemcitabine combinations over gemcitabine alone (relative risk reduction of 9, 4 and 3% at 6, 12 and 18 months, respectively) [31]. A third meta-analysis combined individual patient data from 503 patients enrolled in either the GERCOR/GISCAD Intergroup trial comparing gemcitabine with gemcitabine and oxaliplatin or the German multicenter trial comparing gemcitabine with gemcitabine and cisplatin. Overall survival was significantly better in patients receiving a gemcitabine–platinum analog, hazard rate = 1.23, $P = 0.031$ and median survival = 8.3 versus 6.7 months [32].

Three- and four-drug regimens also have been evaluated in patients with metastatic pancreatic cancer. A small phase III trial compared a four-drug regimen consisting of cisplatin, epirubicin, gemcitabine and 5-FU (PEFG) in comparison with single-agent gemcitabine [33]. The difference in response rate, 38 versus 8.5% and progression-free survival at 4 months, 60 versus 28%, $P = 0.003$ was statistically significant and favored the experimental arm. One-year overall survival for PEFG was 38% compared with 21% with single-agent gemcitabine, but this did not reach statistical significance, $P = 0.11$. Another regimen consisting of capecitabine, gemcitabine and docetaxel demonstrated a response rate of 40% and a median survival of 8.6 months in a retrospective analysis [34].

The present study was designed to determine whether G-FLIP can increase response rate and CBR in patients with advanced or metastatic pancreatic cancer. The initial choices of 10% as the baseline DCR and 30% as the alternative rate were probably too low in light of other studies that showed DCR of 44% for single-agent gemcitabine. The DCR of 67% attained by G-FLIP, however, compares favorably with the 44% DCR

associated with single-agent gemcitabine, and is comparable to DCR reported by other studies using multiagent programs such as PEFG and GTX [1,33,34]. TTP also was significantly prolonged, 6.1 compared with 2.3 months, as observed with single-agent gemcitabine. The response rate and survival outcomes of the six patients from the phase I portion of this trial who received less than MTD irinotecan were comparable to the other patients, so the lower-dose irinotecan did not compromise the results of this study. Whereas the similar outcomes across irinotecan doses may raise doubt regarding the contribution of this drug to G-FLIP, another reasonable hypothesis is that the minimum effective irinotecan dose has not been defined for this regimen.

Although the number of patients evaluable for the composite endpoint of CBR is small, $n = 23$, the 36% rate also compares favorably with the 23.8% reported with single-agent gemcitabine. CBR is a relevant endpoint in patients with pancreatic cancer where it has been difficult to improve not just survival outcomes but also symptom palliation.

CA 19-9 decrease of more than 50% was observed in 11 of the 15 patients evaluable for serological response. Consistent with other reports, a greater than 50% decrease in CA 19-9 was significantly associated with prolonged disease-free and overall survival outcomes [35,36]. CA 19-9 requires further development as a surrogate for clinical outcome in patients with advanced pancreatic cancer, but it does seem to predict improved outcomes across a spectrum of cutoff points. In a cohort of 76 patients, CA 19-9 declines of 25, 50 and 75% were all associated with significant improvements in failure-free survival and overall survival outcomes [35].

Grade 3 and 4 toxicities seen with this regimen were comparable to toxicities observed with single-agent gemcitabine or with combination regimen such as gemcitabine and oxaliplatin as shown in Table 4. The comparable hematological toxicity profiles can be explained by the difference in gemcitabine dose of 1000 mg/m^2 every 4 weeks with G-FLIP versus 3000 mg/m^2 every 4 weeks with single-agent gemcitabine. The incidence of grade 3/4 nausea, vomiting and diarrhea also was less than reported with single-agent gemcitabine, probably secondary to aggressive use of antiemetics and antidiarrheals. All toxicities are reported on a per patient basis rather than on a per cycle basis. This is an important distinction. For example, although gastrointestinal toxicities were seen in 69% of patients, this side-effect delayed treatment in only 1% of all cycles.

The optimal dose intensity and schedule of gemcitabine alone and gemcitabine-based combinations is being defined, but there is increasing evidence to support biweekly (every other week) dosing. A phase II study of 43 patients with metastatic pancreatic cancer treated with gemcitabine 2200 mg/m^2 given as a 30-min intravenous infusion every other week reported a TTP of 5.3 months, a median survival of 8.8 months and 1-year survival of 26.3% [37]. In a phase II study of low-dose cisplatin 20 mg/m^2 with gemcitabine 1000 mg/m^2 given as a fixed dose rate infusion 10 mg/m^2/min on days 1 and 8 of a 21-day cycle, two-thirds of study participants (62.7%) required adjustment of their dosing schedule to an every-other-week schedule. The most common reason for transitioning to a biweekly schedule was neutropenia. The median time to schedule change was after two cycles of treatment. Patients switched to biweekly therapy received a median of six treatment cycles compared with a median of only two cycles in the cohort that remained on the original dosing schedule [38]. The cost of two cycles or 1 month of G-FLIP, on the basis of 2006 average wholesale prices, is US$4060 for a 1.8-m^2 patient. By comparison the cost is approximately US$4500 for three weekly gemcitabine 1000 mg/m^2 doses.

The main drawbacks of the G-FLIP regimen are the requirement of central venous access and the lengthy outpatient 2-day treatment design. This trial also has a small sample size and oligo-institutional participation. Although selection bias always is of concern in this setting, the median KPS of 70–80 and American Joint Committee on Cancer stage 4 status of all our patients is comparable to that reported in other trials. Another concern is that sequential use of these drugs as single-agent may be equivalent or of superior benefit to the outcomes attained with G-FLIP. Certainly, in chemosensitive solid tumors, such as breast cancer, palliative use of combination chemotherapy has not proven to have a survival benefit over sequentially administered single agents [39]. This paradigm, however, is not applicable to chemo-resistant tumors such as nonsmall cell lung cancer and colorectal carcinomas [40,41].

Another anticipated criticism of the G-FLIP regimen is that it includes drugs that have not improved survival outcomes when combined with gemcitabine. To dismiss drugs from further development against advanced pancreatic cancer on this basis is, however, a mistake. For example, oxaliplatin and infusional 5-FU has demonstrated overall survival benefit in patients with advanced pancreatic cancer that has progressed on prior gemcitabine when compared with best supportive care alone, 21 versus 10 weeks from initiation of second-line therapy, *P*-value 0.0077 [42].

G-FLIP is a regimen with a high response rate and acceptable toxicity. Future placement of this regimen in the pancreatic cancer treatment algorithm remains a research question. The evolution of this regimen will

include substituting oxaliplatin (Eloxatin) for cisplatin. A phase I dose finding trial in which cisplatin is replaced by oxaliplatin, so-called G-FLIE, has identified biweekly oxaliplatin 85 mg/m^2 as the MTD [43]. G-FLIE may represent a more active four-drug regimen given the demonstrated, significant survival benefit of infusional 5-FU and oxaliplatin in patients with metastatic pancreatic cancer that has progressed on prior gemcitabine [42].

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