Phase I dose-finding study of biweekly irinotecan in combination with fixed doses of 5-fluorouracil/leucovorin, gemcitabine and cisplatin (G-FLIP) in patients with advanced pancreatic cancer or other solid tumors

R. Rachamalla[a], S. Malamud[b], M. L. Grossbard[a,b], S. Mathew[a], M. Dietrich[b] and P. Kozuch[a]

This phase I trial was initiated based on encouraging clinical data with 5-fluorouracil (5-FU)/leucovorin (LV), gemcitabine and cisplatin (G-FLIP) in the therapy of solid tumors. In this trial, G-FLIP has been modified to facilitate outpatient administration and to optimize sequence-dependent synergistic activity. Treatment consisted of biweekly (once every 14 days) cycles of sequential gemcitabine 500 mg/m^2, irinotecan per dose escalation schedule, bolus 5-FU 400 mg/m^2 and LV 300 mg on day 1 followed by a 24-h 5-FU infusion 1500 mg/m^2, followed by cisplatin 35 mg/m^2 on day 2. The irinotecan starting dose was 80 mg/m^2 and escalated by 20 mg/m^2 in cohorts of three patients until the maximum tolerated dose (MTD) was defined. Twenty-three patients were enrolled (13 men/10 women) with the following cancers: 11 pancreatic, five gallbladder, three squamous cell carcinoma of the head and neck, one hepatocellular carcinoma, one melanoma, one gastric, and one breast cancer. Median patient age was 63 years (range 44–78) and median Karnofsky performance status (KPS) was 80. Patients received a median of 8 cycles (range 1–16) over five irinotecan dose levels (80, 100, 120, 140 and 160 mg/m^2). Dose-limiting toxicity consisting of grade 3 nausea/vomiting despite aggressive anti-emetic therapy occurred in one patient at dose level 1 and three patients at dose level 3. Grade 3–4 hematological toxicities per patient consisted of thrombocytopenia (3%), anemia (6%), thrombosis (23%), neutropenia (16%) and neutropenic fever (10%). Of 18 patients evaluable for response, one complete response (pancreatic) and eight partial responses (three gallbladder, two pancreatic, two head and neck, and one breast) were attained. Seven patients had disease stabilization (five pancreatic, one hepatocellular and one gastric) for a median of 16 weeks (range 10–22). Median time to disease progression among all 23 patients enrolled to the phase I portion of the trial was 20.5 weeks (range 4–37). We conclude that G-FLIP is a novel outpatient chemotherapy regimen with acceptable toxicity at the maximum tolerated irinotecan dose of 120 mg/m^2. The phase II trial of G-FLIP using an irinotecan dose of 120 mg/m^2 for patients with metastatic pancreatic cancer is ongoing. *Anti-Cancer Drugs* 15:211–217 © 2004 Lippincott Williams & Wilkins.

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[a]St Luke's-Roosevelt Hospital Center, New York, NY, USA and [b]Beth Israel Medical Center, New York, NY, USA.

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Correspondence to P. Kozuch, St Luke's-Roosevelt Hospital Center, 1000 10th Avenue Suite 11G, l New York, NY 10019, USA.
Tel: +1 212 523-6769; fax: +1 212 523-2004;
e-mail: pkozuch@chpnet.org

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Introduction

The novel combination of gemcitabine, 5-fluorouracil (5-FU) bolus plus infusion, irinotecan and cisplatin (G-FLIP) was developed to approximate known sequence-dependent activity while minimizing sequence-dependent toxicity among the four drugs. A retrospective analysis of a similar regimen containing these four drugs demonstrated encouraging activity and survival outcomes in heavily pretreated patients, all with metastatic pancreatic cancer, thereby encouraging phase I and II development of the regimen with a simplified 5-FU schedule [1].

Irinotecan (CPT-11, Camptosar) is a water-soluble topoisomerase I inhibitor with a unique mechanism of action of reversible inhibition of DNA topoisomerase I and a broad range of antitumor activity as a single agent [2]. Topoisomerase I inhibitors also may interfere with processes involved in DNA repair and enhance cytotoxicity when combined with DNA-damaging agents such as cisplatin. Overlapping single-agent activity, non-overlapping toxicities, and a lack of cross-resistance and potential synergism in preclinical studies provide the rationale for combining irinotecan and cisplatin [3–5]. Several phase I trials have demonstrated the feasibility of combining these two drugs in a variety of dosages, schedules and sequences. Phase I and II data support total monthly cisplatin doses of 60–80 mg/m^2, and monthly irinotecan doses between 180 and 280 mg/m^2 independent of

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dose scheduling (i.e. weekly, biweekly, monthly dosing) [6]. There is clinical evidence suggesting reversal of cisplatin resistance when it is combined with irinotecan [7].

Gemcitabine is a cell-cycle-specific pyrimidine nucleoside analog that undergoes intracellular phosphorylation to form active di- and triphosphates. This process is dose rate dependent so the effectiveness of gemcitabine may be improved by altering the standard infusion schedule to a fixed-dose rate [8]. Gemcitabine cytotoxicity correlates with its incorporation into genomic DNA thereby inhibiting DNA synthesis.

5-FU is an anti-metabolite that also requires intracellular activation to inhibit DNA synthesis. Preclinical and clinical data have reported cytotoxic synergy between gemcitabine and 5-FU in pancreatic and ovarian cancers [9]. Several phase I–II studies using different infusion schedules of 5-FU in combination with gemcitabine have reported potentially additive activity for the combination in pancreatic and renal cell carcinoma with tolerable toxicity profile [10–13].

Irinotecan can be combined safely with gemcitabine and the doublet has demonstrated response rates of 20–30% in patients with locally advanced or metastatic pancreatic cancer. Toxicities include grade 3–4 neutropenia and grade 3 diarrhea [14,15]. Combinations of cisplatin with either 5-FU or gemcitabine have been studied extensively in various malignancies including esophageal, lung, cervix, head and neck, and urothelium.

The G-FLIP regimen is based on laboratory evidence of disease-specific drug synergism with irinotecan. A retrospective analysis of 34 heavily pretreated metastatic pancreatic cancer patients treated with G-FLIP combination (irinotecan dose = 80 mg/m^2) reported a partial response rate of 24%, disease stabilization rate of 21% and a median survival of 10.3 months. The regimen was well tolerated with most observed toxicities being grade 1–2 mucositis, nausea/vomiting, neurotoxicity, nephrotoxicity and diarrhea [1]. A review of 15 patients receiving the four-drug regimen as initial treatment of metastatic pancreatic cancer documented a 33% response rate [17]. Based on this encouraging clinical activity, a phase I dose-finding study was initiated to determine the maximum tolerated dose (MTD) of irinotecan in combination with fixed doses of gemcitabine, 5-FU/leucovorin (LV) and cisplatin in metastatic solid tumors.

Materials and methods

Patient selection

Patients with a histologically or cytologically confirmed diagnosis of a solid tumor refractory to conventional treatment or for which no standard therapy existed were eligible for this phase I study. Once MTD was defined, accrual was transitioned to the phase II trial and enrollment was limited to patients with metastatic pancreatic cancer. Other eligibility criteria included the following: age $\geq$ 18 years, Karnofsky performance status (KPS) of $\geq$ 60, life expectancy of at least 12 weeks; no chemotherapy, immunotherapy or radiotherapy for at least 4 weeks prior to entry into the study (6 weeks for nitrosureas or mitomycin C); no concurrent therapy including chemotherapy, immunotherapy, radiotherapy or any other investigational drug; no prior therapy with a topoisomerase I inhibitor; measurable or evaluable disease; adequate hematopoietic (absolute granulocyte count of $\geq$ 1500/mm^3 and platelet count $\geq 100 \times 10^9$/l), renal (creatinine of $\leq$ 1.5 mg/dl) and hepatic function (bilirubin $\leq$ 2.0 mg/dl); negative pregnancy test documented prior to study entry for premenopausal women; men and women who were fertile must have used adequate contraception. Exclusion criteria included patients with brain involvement or leptomeningeal disease; progressive sensory neuropathy or hearing loss; serious illnesses or medical conditions including uncontrolled diabetes, hypertension or arrhythmias, congestive heart failure or unstable angina, active infection, prior invasive malignancies within 5 years with an exception of curatively treated basal or squamous cell carcinoma of skin or carcinoma in situ of the cervix. A signed informed consent was obtained from all patients before study entry. The protocol had approval of a local IRB.

Dosage and drug administration

Therapy was administered in an outpatient setting every 2 weeks and consisted of gemcitabine 500 mg/m^2 i.v. in 100 cm^3 normal saline at 10 mg/m^2/min, followed by irinotecan (per dose escalation schema) in 500 cm^3 D5W over 90 min, followed by LV 300 mg in 50 cm^3 normal saline i.v. over 10 min, followed by 5-FU 400 mg/m^2 in 50 cm^3 normal saline over 10 min, followed by 5-FU 1500 mg/m^2 via an AIM pump (Ambulatory Infusion Manager; Abbott, Chicago, IL) over 24 h on day 1. On day 2, 24 h after the day 1 5-FU bolus, patients received 35 mg/m^2 of cisplatin in 50 cm^3 normal saline i.v. over 45 min.Prior to receiving cisplatin, mannitol 12.5 g was administered i.v. in 500 cm^3 D5 0.5 normal saline over 30 min and an additional 25 g of mannitol in 1000 cm^3 0.5 normal saline with 30 meq of potassium chloride (KCl) and magnesium sulfate 2 g was administered upon completion of cisplatin infusion. Cisplatin infusion was started once urine output reached at least 100 cm^3/h with 10–20 mg of lasix given immediately before cisplatin infusion. The starting irinotecan dose was 80 mg/m^2 and was escalated stepwise by 20 mg/m^2 increments in successive cohorts of three patients until the MTD was reached. Additional patients could be enrolled at a particular dose level to further evaluate toxic side-effects.

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At each dose level, the initial patient was observed for 4 weeks (2 biweekly cycles) prior to entry of subsequent patients. Subsequent patients at each dose level were evaluated weekly for at least 2 weeks before accrual at the next dose level could take place. Weekly evaluations consisted of a toxicity check, physical examination and laboratory evaluation (complete blood count, chemistry profile including serum creatinine, electrolytes and hepatic function).

Assessment of toxicity and response

Dose-limiting toxicity (DLT) was defined as grade 3 or greater non-hematologic toxicity (including nausea/vomiting despite aggressive antiemetic therapy) or inability of the patient to take 75% or more of planned chemotherapy. If DLT developed in one of three patients, then three additional patients were to be enrolled at that dose level. If two or three out of three initial patients or more than one out of three additional patients treated at a dose level developed DLT, dose escalation was to be stopped. MTD was defined as the dose level below the dose that produced unacceptable toxicity. Additional patients were to be enrolled at the MTD in the phase II portion of the study to further characterize disease specific efficacy and toxicity.

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. Cisplatin dose was decreased by 25% for neutropenic fever, platelet counts $\leq 100\,000/m^3$ or for grade 1–2 persistent sensory neuropathy. Cisplatin was discontinued for grade 3–4 sensory neuropathy. Cisplatin dose was reduced to 20 mg/m^2 and administration changed to a continuous infusion if serum creatinine rose to 1.5–3 mg/dl. Infusional 5-FU dose was reduced by 25% for grade 3–4 stomatitis or grade 2 or greater hand–foot syndrome. Irinotecan-associated acute or delayed diarrhea was treated symptomatically with atropine and loperamide, and irinotecan dose was reduced by 25% for grade 3–4 diarrhea.

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 studies such as computed tomography scans or magnetic resonance imaging. A complete response (CR) was defined as the disappearance of all measurable and evaluable disease for at least 4 weeks without appearance of new lesions. A partial response (PR) was defined as at least 30% decrease in the sum of longest diameter of all measurable lesions from baseline without appearance of new lesions. Progressive disease (PD) corresponded to at least 20% increase in the sum of the longest diameter of the measurable lesions or the appearance of new lesions. Stable disease (SD) was defined as insufficient decrease in tumor to qualify for a PR or insufficient increase in size to qualify for PD. Toxicity was evaluated in patients who received at least two G-FLIP cycles. Patients who achieved a CR could continue treatment for up to 6 months beyond the documentation of complete response. All patients with PR or with SD were continued until documentation of disease progression. Patients were withdrawn from the therapy in case of progressive disease, patient refusal, physician's preference or development of any toxicity that would preclude further therapy. Response durations were measured from the time of documented radiographic response to the first observation of progressive disease. Time to disease progression was measured from the start of the treatment to first documentation of disease progression.

Study design

This study was designed as a phase I–II, open label, non-randomized dose finding study. In the phase I study, the first three eligible patients were assigned to receive treatment at dose level 0. At least three patients were studied for 28 days at each dose level before starting additional patients on escalated doses of irinotecan. In the event that the MTD was less than irinotecan 100 mg/m^2 biweekly the dose of cisplatin was to be reduced to 30 mg/m^2 biweekly and irinotecan dose escalation would resume at one dose level below the previous MTD. When the MTD of irinotecan was determined, accrual was to be transitioned to the phase II aspect of the trial. Accrual to the phase II study was limited to patients with metastatic pancreatic cancer in order to fully define disease specific efficacy as well as to further characterize the toxicity profile of this novel regimen.

Results

Patient characteristics

Twenty-three patients were enrolled in the phase I study between March 2002 and February 2003. Patient characteristics are illustrated in Table 1. Thirteen men and 10 women with a median age of 63 years and median KPS of 80 were enrolled. Ten patients (43%) received prior treatment: two patients received surgery alone, two patients received either chemotherapy alone or in combination with surgery, one patient received chemotherapy and radiation, and five patients received surgery, chemotherapy and radiation. All 23 patients enrolled into the phase I study were assessable for toxicity after completing a minimum 2 cycles of therapy. Eighteen of these patients were evaluable for response. Five patients were withdrawn from the trial prior to response evaluation for the following reasons: one patient had severe asthenia necessitating withdrawal from study after 1 cycle and four patients had early disease progression after 1 or 2 cycles of G-FLIP. The initial seven patients with metastatic pancreatic cancer enrolled in the phase II portion of this trial are evaluable for

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toxicity. Four were men and three women; median age was 54. Five of these patients previously were untreated and two had received prior gemcitabine-based regimens.

Treatment administration and toxicity

A total of 134 cycles were administered and each patient received a median of 8 cycles (1–16). From a starting dose of 80 mg/m^2 of irinotecan, dose escalation proceeded until dose level 4 (160 mg/m^2). Hematologic and non-hematologic toxicities are summarized in Table 2. No DLTs were identified at dose level 0, and one out of three patients at dose level 1 required hospitalization for nausea and vomiting. Subsequently, three additional patients were enrolled at dose level 1 without additional DLTs. All patients at dose level 2 tolerated therapy without DLTs. Six patients initially were enrolled at dose level 3, per protocol, permitting accrual of additional patients at a particular dose level to further evaluate toxic side-effects. One of these six patients developed grade 3 nausea and vomiting requiring hospitalization and i.v. hydration. Therefore, an additional three patients were enrolled at dose level 3, two of whom developed refractory grade 3–4 nausea/vomiting requiring hospitalization in spite of aggressive antiemetic therapy. At the principal investigator's discretion, one patient was entered at dose level 4 before the DLT and MTD were determined. Grade 2 nausea and vomiting occurred at that dose. In light of the above events, dose level 2 was identified as the MTD. Per study design, accrual was then transitioned to the phase II part of the study. The initial seven patients enrolled onto the phase II trial were evaluable for toxicity and none experienced DLT.

Table 1 Phase I patient characteristics

Characteristic	No. of patients	%
No. entered	23	100
Sex		
male	13	56
female	10	44
Age (years)		
median	63	
range	44–78	
Performance status (KPS)		
60	1	4
70	3	13
80	11	48
90	6	26
100	2	8
Prior therapy[a]		
none	13	56.5
surgery alone	2	8.6
surgery, chemotherapy and radiation	5	21.7
chemotherapy and radiation	1	4
surgery and chemotherapy	1	4
chemotherapy alone	1	4
Primary site		
pancreas	11	47
gallbladder	5	21
hepatocellular	1	4
head and neck	3	13
gastric	1	4
melanoma	1	4
breast	1	4

[a]Other prior treatments included interferon in one patient.

Outside of the DLT, therapy was well tolerated and grade 3–4 toxicities per patient were largely hematological, and consisted of anemia (6%), thrombocytopenia (3%), neutropenia (16%) and neutropenic fever (10%). Hematologic toxicities were consistent throughout all dose levels. Grade 3–4 thrombosis occurred in seven patients (23%), so the protocol was amended with prophylactic coumadin 1 mg daily recommended. Grade 3–4 non-hematologic toxicities were limited to nausea/vomiting and fatigue in four (13%) and seven patients (23%), respectively. Grade 3–4 nausea/vomiting was observed in one patient at dose level 1 and three patients at dose level 3. Other non-hematologic toxicities were mainly grade 1–2 nausea/vomiting (60%), diarrhea (40%), constipation (16%) and fatigue (30%). Grade 1–2 ototoxicity and neurotoxicity was seen in two patients. Two patients developed cisplatin hypersensitivity, during cycles 5 and 11, respectively. These hypersensitivity reactions were characterized by intense chest pressure and light-headedness in one patient, and chest pressure and diffuse skin erythema in the other patient. Both of these reactions

Table 2 Toxic side-effects (event per patient)

	Dose level 0 (n=4)		Dose level 1 (n=6)		Dose level 2 (n=10)		Dose level 3 (n=9)	
	Grade 3–4	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4	Grade 1–2
Hematological								
neutropenia	0	0	3	2	1	0	1	0
thrombocytopenia	0	0	1	1	0	1	0	0
anemia	1	NR	1	NR	0	NR	0	NR
neutropenic fever	0	NA	2	NA	0	NA	1	NA
thromboembolism	1	NA	4	NA	1	0	1	NA
Non-hematological								
neuropathy	0	0	0	1	0	1	0	0
ototoxicity	0	0	0	2	0	0	0	0
constipation	0	0	0	3	0	1	0	1
nausea/vomiting	0	2	1	5	0	7	3	4
fatigue	0	1	2	2	3	3	2	3
diarrhea	0	0	0	2	0	5	0	5

NR, not reported; NA, not applicable.

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occurred within the first minute of cisplatin infusion, and recurred despite appropriate premedication with steroids and diphenhydramine upon rechallenge. Cisplatin was, therefore, discontinued in these two patients.

Tumor response

Eighteen of 23 patients were evaluable for response. One patient with locally advanced pancreatic cancer attained a radiological CR after 4 cycles of therapy and remained in CR following 8 cycles. Eight patients (44%) had PRs: three patients with gallbladder cancer, two with pancreatic cancer, one patient with adriamycin/taxane refractory breast cancer, and two patients with platinum/taxane refractory head and neck cancer (tongue and sinus). Seven patients (39%) attained disease stabilization: five pancreatic, one hepatocellular and one gastric cancer. Median time to disease progression among all 23 patients was 20.5 weeks (range 4–37 weeks).

Discussion

The chemotherapy agents in G-FLIP all have proven single-agent activity in a wide variety of malignancies. A clear rationale exists for combining these drugs based on preclinical and clinical data. Three drug and four drug regimens have been evaluated in pancreatic cancer. A retrospective analysis of 49 patients with advanced pancreatic cancer treated with gemcitabine, 5-FU/LV and cisplatin reported a median survival of 10.6 months and a 1-year survival of 46%. Grade 3–4 toxicities were hematological [18]. A four-drug combination of cisplatin and epirubicin on day 1, gemcitabine on days 1and 8, and 5-FU continuous infusion daily for 28 days given to patients 49 with advanced pancreatic cancer (43 patients had metastatic disease) reported an objective response rate of 58% and clinical benefit in 22 (78%) of 28 assessable patients. The median survival was 10 months in the intent-to-treat population [19].

Table 3 illustrates the increasing response rates and overall survival associated with combination chemotherapy, providing the rationale for multidrug combinations in pancreatic cancer. Most phase II trials of gemcitabine-based doublets have reported median survivals of 7.5–8.5 months, but these modest advances did not withstand analysis in phase III trials [20–23]. However, median survivals of 10–11 months are consistently reported in phase II trials of three- and four-drug regimens. These survival outcomes may represent a threshold that will translate into clinically meaningful advances in phase III testing.

This trial was a phase I dose escalation study designed to determine the MTD of irinotecan in combination with fixed doses of gemcitabine, 5-FU/LV and cisplatin given as an outpatient regimen on an every-2-weeks schedule in patients with advanced solid tumors. The DLT was 5-HT_3 antagonist-refractory nausea and vomiting occurring at irinotecan dose level 3 (irinotecan = 140 mg/m^2). Cisplatin was dose reduced by 25% in only two patients due to delayed emesis. The subsequent FDA approval of aprepitant for delayed chemotherapy-associated nausea and vomiting may improve the tolerability of this regimen. Other non-hematologic toxicities were mild. Except at dose level 0 (irinotecan 80 mg/m^2), grade 3–4 neutropenia occurred at a rate of 33% of patients/dose level. Grade 3 anemia requiring transfusions occurred in 9% of patients. Hematopoietic colony stimulating factors like filgrastim or sargramostim and erythropoietin were administered according to the indications set forth by American Society of Clinical Oncology [24]. Grade 3 thrombocytopenia was seen in two patients and was self limiting without bleeding complications or need for platelet transfusion. Hypersensitivity reactions to i.v. cisplatin are a rare, but life-threatening, complication that may occur even in patients who have received prior treatment with cisplatin. The appearance of hypersensitivity reactions was reported in patients treated with concomitant pelvic radiation and weekly i.v. cisplatin for gynecologic malignancies [25].

The 31% incidence of thrombotic events with five patients developing deep venous thrombosis and two patients presenting with uncomplicated pulmonary embolism is notable. All patients with thrombotic events were treated with therapeutic doses of low-molecular-weight heparin. Hypercoagulability in cancer patients

Table 3 Phase II reports of two-, three- and four-drug regimens for locally advanced and metastatic pancreatic cancer

Treatment	No. patients	LA/M (%)	RR (%)	Median PFS (months)	Median OS (months)	Reference
Gem (phase III)	163		5.6	2.2	5.4	20
Gem/5-FU bolus	164	10/90	6.9	3.4	6.7	
Gem 10 mg/m^2/min/5-FU bolus	34	24/76	17	3.7	5.7	29
Gem + 5-FU bolus and infusion (FOLFUGEM)	62	35/65	26	4.8	9.0	30
Gem + cisplatin biweekly	35	15/85	11.5	4.3	8.3	31
Gem + oxaliplatin	34	0/100	31	4.1	8.7	32
Gem + irinotecan	45	28/72	20	2.8	5.7	14
Gem/5-FU/cisplatin	49	0/100	16.3	2.1	10.6	18
Gem/5-FU/irinotecan/cisplatin	34	0/100	23.5	2.5	10.3	1
Gem/cisplatin/epirubicin/5-FU	49	0/100	58	7.5	10	19
Iriotecan/oxaliplatin/5-FU	23	0/100	50	7.5	NS	33

LA, locally advanced disease; M, metastatic disease; Gem, gemcitabine; NS, not specified.

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remains a complex and poorly understood problem. Activation of factor X, increased fibrinogen and platelet catabolism, decreased protein C, S and antithrombin III as well as direct generation of thrombin have been implicated in this process [26]. In one series from the UK, the estimated prevalence of venous thromboembolism in advanced pancreatic cancer patients was over 50% [27]. It is not known to what extent irinotecan, 5-FU, LV and drug administration schedule contribute to the rate of thromboembolism observed in this trial. During the panel review of CPT-11 trials in colorectal cancer, Rothenberg *et al.* reported a 16% incidence of thromboembolic events with a combination of irinotecan, infusional 5-FU and LV compared to 9% with infusional 5-FU and LV [28]. All subsequently enrolled patients were started on low-dose coumadin for thromboprophylaxis.

Significant antitumor activity in a wide variety of solid tumors including pancreas, gall bladder, hepatocellular, head and neck, and anthracycline/taxane refractory breast cancer was observed. In summary, G-FLIP is a well-tolerated regimen, administered in an outpatient setting on a biweekly basis. This regimen appears to be particularly active in pancreatic and gallbladder cancers. The DLT was intractable nausea and vomiting requiring hospitalization and i.v. fluid support. The recommended dose of irinotecan for phase II study is 120 mg/m^2 in combination with fixed doses of gemcitabine, 5-FU/LV and cisplatin. Phase II testing in pancreatic cancer patients is ongoing.

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