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CLINICAL TRIAL REPORT

The gemcitabine, docetaxel, and capecitabine (GTX) regimen for metastatic pancreatic cancer: a retrospective analysis

Robert L. Fine · David R. Fogelman · Stephen M. Schreibman · Manisha Desai · William Sherman · James Strauss · Susan Guba · Riolan Andrade · John Chabot

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Abstract
Purpose We developed a laboratory based regimen called GTX which induces synergistic apoptosis in human pancreatic cancer cells. This retrospective review summarizes our clinical experience with GTX in an initial group of 35 patients; 66% untreated and 34% failed prior therapies.
Methods All patients treated with GTX for metastatic pancreatic cancer, prior to initiation of a prospective phase II trial of GTX were assessed and followed until death. GTX consisted of capecitabine (X), 750 mg/m^2 p.o. BID on days 1–14, gemcitabine (G) (750 mg/m^2) over 75 min and docetaxel (T) (30 mg/m^2) on days 4 and 11. Thus one cycle of GTX was 14 days with 7 days off for a 21 day cycle. Tumor assessments were repeated every 3 cycles.
Results All 35 patients had metastatic pancreatic cancer (94% liver, 6% lung sites). Grade 3–4 hematological toxicities were: leukopenia and thrombocytopenia—both 14%, and anemia 9%, respectively. The overall response rate of all 35 patients treated with GTX (from 0.5 cycles onward) was 29% (CR/PR) by WHO criteria, and 31% had a minor response or stable disease (MR, SD). At the metastatic sites for the 35 patients, there were 9% complete (CR) and 31% partial (PR) responses (total 40%). For the 31 patients who had their primary tumor (4 patients had a prior Whipple resection), there were 13% CR and 19% PR for a response rate of 32% at the primary tumor site. Overall median progression free survival of responders was 6.3 months (95% C.I. 4.4–10.4 months) and median survival was 11.2 months (95% C.I. 8.1–15.1 months). Survival after initiation of GTX at 12, 18, 24 and 30 months was 43, 29, 20, and 11%, respectively.
Conclusion Our retrospective review suggests that GTX has potential as a regimen for untreated and treated metastatic pancreatic cancer.

R. L. Fine · D. R. Fogelman · W. Sherman
Experimental Therapeutics Program,
Division of Medical Oncology, Department of Medicine,
New York Presbyterian Medical Center,
Columbia University College of Physicians and Surgeons,
and The Pancreas Center at Columbia, New York, NY, USA

S. M. Schreibman
Oncology and Hematology Specialists,
Morristown Memorial Hospital, Morristown, NJ, USA

M. Desai
Department of Biostatistics, Mailman School of Public Health,
New York Presbyterian Medical Center,
Columbia University College of Physicians and Surgeons,
and The Pancreas Center at Columbia, New York, NY, USA

J. Strauss
U.S. Oncology Associates, Dallas, TX, USA

S. Guba
Texas Cancer Associates, Dallas, TX, USA

R. Andrade
Hematology-Oncology Associates,
Poughkeepsie, NY, USA

J. Chabot
Whipple Service, Department of Surgery,
New York Presbyterian Medical Center,
Columbia University College of Physicians and Surgeons,
and The Pancreas Center at Columbia, New York, NY, USA

R. L. Fine (✉)
Division of Medical Oncology,
Columbia University Medical Center,
650 West 168th Street, Room 20-05,
New York, NY 10032, USA
e-mail: rlf20@columbia.edu

Introduction

Pancreatic cancer has become the fourth most common cause of cancer related deaths, surpassing prostate cancer [1]. Five year survival is less than 5%, irrespective of initial stage. Approximately 90% of patients who present with advanced pancreatic cancer survive less than one year and median survival of metastatic patients treated with chemotherapy is approximately 5–6 months.

Gemcitabine (2′,2′-difluorodeoxycytidine), a nucleoside analog which induces DNA chain termination and potent inhibition of ribonucleotide reductase, is the standard of care. Gemcitabine was the first drug to increase median survival in pancreatic cancer, albeit by only 5 weeks, over 5-FU [2]. A seminal phase III trial by Burris et al. randomized 126 patients to either weekly gemcitabine over 30 min or weekly IV 5-FU. Both median survival (5.65 vs. 4.41 months) and clinical benefit (a measurement of analgesic use and weight) were statistically superior in the gemcitabine arm. Response rates were not statistically different, though gemcitabine produced more responses (5.4 vs. 0%) and more disease stability (39 vs. 19%) as compared to 5-FU [2]. Gemcitabine has been studied in a prolonged infusion schedule at 10 mg/m^2/min based upon the seminal work by Brand et al. [3], and Tempero and Abbruzzese [4] which demonstrated improved phosphorylation and activation of gemcitabine by deoxycytidine kinase with prolonged infusion times. Tempero et al. [4] demonstrated in a randomized phase II trial that overall survival in patients treated at this rate was greater than in patients treated with a 30 min infusion of higher dose gemcitabine. Based on this pharmacological principle, we incorporated the fixed dose rate (FDR) infusion of gemcitabine into the GTX regimen.

Over the past few years, a number of gemcitabine-based doublets have been tested to improve response rate and survival of patients with advanced pancreatic cancer. Examples include gemcitabine with cisplatin, oxaliplatin, irinotecan, 5-FU, capecitabine, docetaxel and erlotinib. In completed phase III studies, response rates were generally higher in the doublet groups. However, in yet unpublished phase III studies, only combinations of gemcitabine with erlotinib or a 21 day schedule of capecitabine with weekly gemcitabine have demonstrated minor to modest improvements in median survivals over gemcitabine alone [5, 6].

Capecitabine was substituted for fluorouracil in GTX because: (1) capecitabine, on an every 12 h schedule mimics continuous infusion 5-FU; (2) preferential conversion of 5-dFUR to 5-FU in tumor cells by thymidine phosphorylase (TP) which activates capecitabine to 5-FU and is more highly expressed in tumor than normal cells of the same histology; (3) docetaxel upregulates TP levels in some cancer cells, enhancing conversion of capecitabine to 5-FU, and (4) ease of administration.

This is the initial report of our experience with the GTX regimen [7, 8]. We have retrospectively assessed all patients treated with GTX (#35) prior to initiation of our prospective phase II study. All patients were treated at Columbia University Medical Center and in community practices, ranging from 0.5 cycles of GTX onward. Thus, this review includes all patients who received any part of the GTX regimen (0.5 cycles) to multiple cycles of GTX.

Methods

Patient selection

From January 2001 to January 2003, 35 patients (Table 1) with metastatic pancreatic cancer were treated with GTX upon proof of histologic diagnosis of adenocarcinoma of the pancreas that was confirmed at Columbia University Medical Center. Entry criteria for treatment required that pancreatic neuroendocrine tumors were ruled out by immunohistochemistry. Patients were not excluded for poor performance status (ECOG 1–3). A minimum leukocyte count of 3,000/mm^3, platelet count of 100,000 $\times$ 10^3, and *any* liver function test abnormalities were accepted for GTX treatment except the total bilirubin had to be $\leq$ 2.0 mg/dl because of the enterohepatic circulation of the natural product agent docetaxel. Pretreated patients had to be 3 and 4 weeks off of any previous chemotherapy or radiation, respectively.

Table 1 Patient characteristics

Median age	59
Age range	37–85
Male/female (%)	55/45
Treated Columbia/community	66/34%
Median CA 19-9	1,738
Mean CA 19-9	72,985
Range CA 19-9	17–700,000
Median CEA	16
Mean CEA	156
Range CEA	0.6–2,302
Percent pre-treated	34%
Median # regimens	1
Range # regimens	1–>4
Degree of differentiation	
Well	3 (9%)
Moderate	14 (40%)
Poor	9 (26%)
Not assessable[a]	9 (25%)

[a] FNA with no grading

Treatment regimen

One cycle of GTX was given over 14 days consisting of capecitabine (X), 750 mg/m^2 p.o. BID on days 1–14 (total 1,500 mg/m²/day), with gemcitabine (G) (750 mg/m^2 over 75 min) followed by docetaxel (T) (30 mg/m^2 over 60 min) on days 4 and 11 given IV (GTX). The third week (days 15–21) was without treatment. The dosing of drugs in GTX were derived from: (1) our previous prospective phase II trial of docetaxel and gemcitabine in advanced pancreatic cancer patients [9], (2) a reduced dosing of capecitabine derived from previous reports where capecitabine was given with gemcitabine [10]; and (3) our laboratory studies, mentioned in the Discussion, where we demonstrated that capecitabine produced synergistic cell kill in pancreatic cancer lines when previously added to docetaxel and gemcitabine [11, 12]. No other chemotherapies, surgery, radiation or holistic medicines were given while on GTX.

Doses of drugs were typically only adjusted for grade 3/4 toxicities. Hematologic toxicity was addressed by first reducing the dose of gemcitabine by 25% (from 750 mg/m^2 to 560 mg/m^2) with all doses delivered at 10 mg/m²/min. Capecitabine dosing was reduced 25% for grade 2 and 50% for grade 3 mucositis, diarrhea, or hand-foot syndrome (HFS). Docetaxel dosing was reduced 25% when hematologic grade 3–4 toxicity occurred despite a 25% reduction of gemcitabine and initiation of growth factors, (docetaxel was reduced 25% in only 2 of the 35 patients). Thus, growth factors (G-CSF, GM-CSF) were systematically initiated for persistent hematologic grade 3/4 toxicity despite a 25% reduction of gemcitabine dosing before reduction of docetaxel occurred. The maximum reduction of gemcitabine, docetaxel and capecitabine for count suppression or HFS, respectively, was 50%.

Patients received low molecular weight heparinoids and not coumadin for venous or arterial thrombosis as described in our publication on the pathophysiology of Trousseau's thromboembolic disease in pancreatic cancer [13].

Assessment of response

Patients were assessed for response after three cycles of GTX (total 9 weeks) and every 3rd cycle thereafter while on therapy. The World Health Organization (WHO) criteria was used for complete response (CR), partial response (PR), minor response (MR), stable disease (SD) and progressive disease (PD). Survival was measured from the first GTX infusion until the date of death. This paper was written when 100% of the patients had died. Imaging and pathology was performed locally and were referred centrally for compilation of results.

Responses were graded by two methods: (1) overall (all sites of tumor) and (2) separately at metastatic and primary sites by WHO criteria. Separation of response sites was done because the desmoplastic reaction in the primary pancreatic cancer can sometimes obscure responses in CT or MRI scans. All responses were judged consistently throughout their courses by either contrast CT or gadolinium MRI at the same institution where baseline radiographic studies were obtained.

Assessment of toxicity

Hematologic toxicity, including leukopenia, anemia, and thrombocytopenia was reviewed centrally. Non-hematologic toxicity was assessed by chart review. The NCI Common Terminology Criteria, Version 3.0, (NCI–CTC, V. 3.0) was used to quantitate all hematologic and non-hematologic toxicities into grades 1–5.

Results

Patient characteristics

The median age at diagnosis was 59 with a range from 37 to 85-years-old. The pathology of the majority of patients (40%) had moderately differentiated tumors (Table 1). Twenty-three of 35 patients were treatment naïve (66%); 12 patients (34%) had previously progressed on a total of 18 cycles of chemotherapy (Table 2). The PS ranged from 1 to 3 (median = 1) and 52% had PS = 1; 28% had PS = 2; 20% had PS = 3. No patient began with a PS of 0. The seven patients starting with an ECOG PS of 3 (20%) all had malignant ascites at entry which required weekly paracentesis. Thirty-four percent (n = 12) were treated by community oncologists outside of Columbia University Medical Center. All patient records were examined independently of the treating physician for assessment of response. All living patients signed consent forms based on HIPAA and IRB guidelines for review of their records. Evaluation of toxicities, responses, and survival was performed centrally. All 35 patients with metastatic pancreatic cancer (94% liver, 6% lung) were assessed for this report who had been treated with any part or dose of the GTX regimen ($\geq$ 0.5 cycles of GTX), from January 2001 to January 2003 (Table 1). Six patients (17%) received $\leq$ 2 cycles of GTX (range 0.5–2.0 cycles) but were included in this retrospective analysis.

Toxicities

As shown in Table 3, grade 3/4 leukopenia and thrombocytopenia each occurred in 14% of patients and grade 3/4 anemia in 9%. G-CSF or GM-CSF was used in 28% of patients, and erythropoietin was used in 34%. G-CSF or GM-CSF were used as per ASCO guidelines for secondary

Table 2 Previous treatments in 12 of 35 patients (34%)

	n (%)
Gemcitabine	4 (11)
Gem-Capecitabine	4 (11)
RT + 5-FU	3 (9)
Gem-CPT-11	3 (9)
Gem-Cisplatin	2 (6)
Capecitabine	2 (6)
Gem-RFS2000	1 (3)
Paclitaxel-Carbo	1 (3)
Gem-5-FU	1 (3)

Table 3 Hematological Toxicities (no deaths from chemotherapy)

	%Gr 1/2	%Gr 3/4
Leukopenia	46	14[a]
Anemia	69	9
Thrombocytopenia	77	14

[a] One patient had neutropenic sepsis

Table 4 Non-hematological toxicities–Grade 3/4

	%
HFS[a]	14
Diarrhea	14
Malaise	11
Abdominal pain	9
Fatigue	9
Stomatitis	9
Rash	9
Nausea	9
Infection	6
Anorexia	6
Dehydration	6
Neuropathy	3
Effusion	3
Thrush	3

[a] Hand-Foot Syndrome or Palmar-Plantar Erythrodyesthesia

prophylaxis to prevent grade 3/4 leukopenia or febrile neutropenia. One patient had a grade 3 infection without the need for hospitalization (3%), one patient was hospitalized for neutropenic fever and sepsis (3%) and two (6%) were hospitalized briefly for dehydration secondary to diarrhea (Tables 3, 4). The hospitalization rate was 9% (three patients). No patients required platelet or red blood cell transfusions. There were no deaths from chemotherapy.

The most frequent grade 3/4 non-hematologic toxicities (Table 4) were diarrhea, including two cases of Clostridium difficile colitis, and HFS (both 14%). Grade 3/4 malaise occurred in 11% and abdominal pain, fatigue, rash, nausea and stomatitis each occurred in 9%. Grade 3/4 anorexia and dehydration each occurred in 6% (#2) of patients. Grade 3/4 neuropathy, pleural effusions and thrush each occurred in 3% (#1) of patients.

Response data

The overall response rate was 29% (10 of 35, all partial). An additional 31% (11 patients) had either stable disease or a minor response (Table 5).

At the metastatic sites, a total of 14 patients (40%) demonstrated a PR or CR (Table 5). Four patients (11%) had a partial response at metastatic sites by cycle 3. By cycle 6, the response rate at the metastatic sites totalled 31% consisting of two CR (6%) and 9 PR (26%) for a total of 11 responses at metastatic sites (31%). By cycle 9, there was a total response rate of 40% at the metastatic sites: 3 (9%) CR and 11 (31%) PR. In addition, seven patients had either a MR or SD (20%) (Table 5). Virtually all patients who had a response (CR, PR) later than 3 cycles demonstrated either a MR or SD or a $\geq$ 50% decrease in CA 19–9 at the cycle 3 evaluation.

Table 5 Patient responses

	#	*n* = 35
Overall responses (primary/mets)[a]		
Number of PR (CR/PR, PR/CR, PR/PR)[a]	10	29%
Number of MR/SD	11	31%
Total PR/MR/SD	21	60%
Metastatic site responses (94% liver, 6% lung)		
Number of CR	3	9%
Number of PR	11	31%
Number of MR/SD	7	20%
Total response rate (WHO criteria of CR/PR)	14	40%
Total CR/PR/MR/SD	21	60%
Total responses by Cycle (CR, PR) at Metastatic Sites		
Cycle 3		11%
Cycle 6		31%
Cycle 9		40%
Primary site responses (by Cycle 9; *n* = 31 with primary tumors)		
	#	*n* = 31
Number of CR	4	13%
Number of PR	6	19%
Number of MR/SD	10	32%
Total response rate (WHO criteria of CR/PR)	10	32%
Total CR/PR/MR/SD	20	64%

[a] Response in primary then metastatic sites. i.e. PR/PR means a PR in both sites

The primary pancreatic tumor site was evaluable in 31 of 35 patients who did not have a prior Whipple procedure. By cycle 9 there were four CR (13%) and six PR (19%) for a 32% response rate at the primary tumor site. In addition, ten patients achieved a MR or SD (32%) at the primary site (Table 5).

The response rate (CR, PR) to GTX in the 12 patients who had progressed on previous chemotherapy was 25% at metastatic sites and 33% at the primary site. For the 23 untreated patients, the response rates (CR, PR) at metastatic and primary sites were 48 and 30%, respectively. The overall response rate (CR/PR) by standard WHO analysis of all sites in previously treated patients and untreated patients was 25 and 30%, respectively.

Median survival for all 35 patients was 11.2 months from the start of GTX (Table 6, Fig. 1). The percentage of patients surviving at 12, 18, 24 and 30 months were 43, 29, 20 and 11%, respectively, after start of GTX (Fig. 1). One patient survived 54 months who originally presented with lung/liver metastases and developed brain metastases 4 years after starting GTX.

As shown in Table 6, median survival of responding patients (CR/PR) at the metastatic sites was 13.5 months (95% C.I. 9.0–29.5). Median survival for patients who had a MR/SD at metastatic sites was 18.1 months (95% C.I. 3.7–30.6). Median survival of patients who had PD at metastatic sites was 3.9 months (95% C.I. 2.1–7.5). Median progression free survival for all responders (CR/PR) was 6.3 months (95% C.I. 4.4–10.4) (Table 6).

Of those responders (CR/PR) whose CA 19–9 level was initially elevated, there was a median decrease of 96% (Table 6). To assess the relationship between initial CA 19–9 levels and survival, we fit a Cox proportional hazards model with log-transformed initial CA 19-9 values as a predictor of survival. Results demonstrated a statistically significant association between high initial values of CA 19-9 (>500) and an increase in hazard ($P = 0.0136$). The median survival of responders at metastatic sites (CR/PR) whose initial CA 19-9 values were less or greater than 500 were 410 days (13.7 months) and 279 days (9.3 months), respectively, from the start of GTX. For patients who had a CA19-9 decrease of $\geq 85\%$ from GTX, the median survival was 385 days (12.8 months) and if <85%, median survival was 171 days (5.7 months).

Responses (CR/PR) in patients at their metastatic or primary sites to GTX did not correlate to the degree of differentiation of their tumors. Eight of the thirty-five patients (23%) experienced a DVT or PE prior to or on GTX treatment. Two patients died of causes related to thrombosis.

Table 6 Survival and CA19-9 outcomes

Survival outcomes	
Median survival in months (95% Confidence Interval)	
All patients in study ($n = 35$)	11.2 (8.1–15.1)
Metastatic site response is CR/PR	13.5 (9.0–29.5)
Metastatic site response is MR/SD	18.1 (3.7–30.6)
Metastatic site response is PD	3.9 (2.1–7.5)
Median progression free survival in months (95% Confidence Interval)	
Metastatic response is CR/PR	6.28 (4.4–10.4)
Percentage of all patients surviving (95% Confidence Interval)	
At 12 months	42.9% (29.2%–62.8%)
At 18 months	28.6% (16.9%–48.2%)
At 24 months	20% (10.3%–38.8%)
At 30 months	11.4% (4.5%–28.7%)
At 36 months	2.9% (0.4%–19.7%)
At 48 months	2.9% (0.4%–19.7%)
CA 19-9 outcomes: patients with elevated levels ($n = 27$)	
Mean initial CA 19-9	72,985
Median initial CA 19-9	1,738
Mean decrease CA 19-9	54%
Median decrease CA 19-9	91%
Mean decrease of responders (CR/PR)	95%
Median decrease of responders (CR/PR)	96%
Mean decrease of progressors (PD)	55%
Median decrease of progressors (PD)	64%

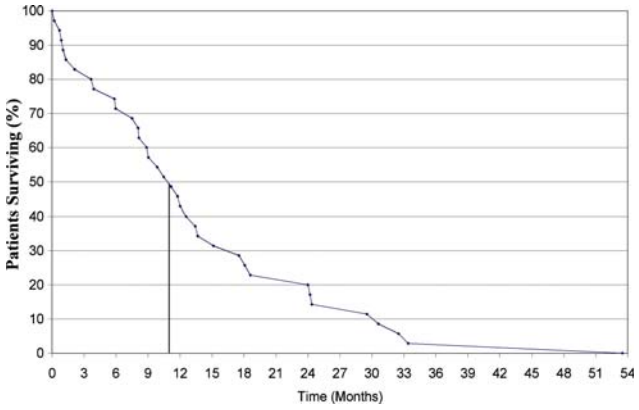

Fig. 1 GTX in Metastatic Pancreatic Cancer. The survival curve of all 35 patients with metastatic pancreatic cancer (94% liver, 6% lung) is presented. All patients were followed from the initiation of GTX till death. One cycle of GTX consists of capecitabine (X) 750 mg/m^2/p.o./BID days 1–14, and gemcitabine (G) 750 mg/m^2/IV over 75 min followed by docetaxel (T) 30 mg/m^2/IV over 60 minutes; both on days 4 and 11. Days 15–21 were off of all drugs. Tumor response was done every 3 cycles. The median overall survival for all 35 patients was 11.2 months (95% confidence intervals of 8.1–15.1 months)

Discussion

The clinical rationale for the GTX regimen

Gemcitabine may be more effective when administered over a protracted infusion period or fixed dose rate (FDR). The rate limiting step is the phosphorylation of the drug to the monophosphate form by deoxycytidine kinase which is maximal at 10 mg/m^2/min [4]. However, the recent randomized phase III ECOG 6201 trial by Poplin et al. [14] was unable to demonstrate a statistically significant survival benefit for the FDR arm, but there was a trend towards improvement over standard dosing and infusion rates for gemcitabine.

Capecitabine has been used as both a single agent and in combination therapy for advanced pancreatic cancer. Response rates as a single agent or with gemcitabine have been between 9.8 and 19%, respectively [10, 15–17]. Median survival in these inoperable and metastatic patients was between 6.4 and 8 months. More recently, Cunningham et al. in a phase III study showed a median survival of 7.4 months utilizing 21 days of capecitabine and 3 weekly doses of gemcitabine, as compared to 6.0 months for gemcitabine alone in 533 patients [6]. Comparatively, there has been a negative phase III trial utilizing capecitabine for 14 days with gemcitabine versus gemcitabine alone [17].

Using docetaxel alone, Rougier et al. [18] and Androulakis et al. [19] reported response rates of 15 and 6%, respectively. We reported a prospective phase II study of metastatic and non-metastatic, inoperable pancreatic cancer patients with docetaxel (90 mg/m²) and gemcitabine (900 mg/m²) over 30 min every 3 weeks with an overall CR/PR rate of 27% and median survival of 8.6 months by intention to treat (ITT) analysis [9]. Schneider et al. reported a similar 27% response rate and 7 month median survival with weekly gemcitabine and docetaxel [20].

Many chemotherapeutic agents have been used in over 12 separate phase II or III doublet combinations with gemcitabine, many of which went on to become negative trials in large phase III studies in pancreatic cancer. These included oxaliplatin [21], cisplatin [22] irinotecan [23], capecitabine [10, 16] and erlotinib [5]. Other multiagent combinations have also been tested with some success: GFLIP (gemcitabine, 5-FU, leucovorin, irinotecan and cisplatin) and GFP regimens [24–26]. Unfortunately, phase III studies by Kindler et al. with bevacizumab and gemcitabine versus gemcitabine and gemcitabine and bevacizumab ± erlotinub ± cetuximab, respectively, did not demonstrate statistical superiority over gemcitabine alone in response rates and overall survival [27, 28]. The ECOG 6201 study reported no statistically significant difference between standard gemcitabine, FDR gemcitabine, and the GEMOX regimen (oxaliplatin + FDR Gem), though there was a trend towards a one month median survival advantage with either FDR gemcitabine or GEMOX [14].

To date, only two phase III studies have shown an increased median survival in combination with gemcitabine. The phase III UK-NCRI study mentioned above by Cunningham et al. [6] demonstrated that 21 days of capecitabine with weekly gemcitabine was superior in overall survival to gemcitabine alone (7.4 vs. 6.0 months) and 1 year survival (26 vs. 19%). The study by Moore et al. [5] demonstrated gemcitabine and erlotinib were superior to standard gemcitabine alone. However, the erlotinib effect was minor, with only a 2 week advantage in overall survival, but with a 10% absolute increase in PFS and SD.

The relatively small improvements with gemcitabine combinations highlight the need for innovative and novel approaches for improving the chemotherapy treatment of pancreatic cancer.

The laboratory rationale for the GTX regimen

Our laboratory data support the combination of all three agents, which will be briefly reviewed here.

The biochemical basis for the lack of superiority of a 14 day regimen of capecitabine or 5-FU with gemcitabine over gemcitabine alone in multiple phase II and III clinical studies is unknown [10, 16, 17, 28–32]. However, we hypothesized that it could be due to scheduling of the 2 drugs. The major effects of 5-FU are inhibition of RNA/DNA synthesis by 5-FUTP and 5-dFUTP and inhibition of thymidylate synthase (TS) by 5-dFUMP which reduces

thymidine pools. Both 5-dFUTP and 5-dFUMP require deoxyribose for their synthesis from 5-FU. However, gemcitabine potently inhibits ribonucleotide reductase leading to reduced deoxyribose pools [2]. Thus, to prevent the hypothetical gemcitabine mediated inhibition of 5-FU metabolism to its active forms, we postulated that 5-FU or capecitabine should be administered for several days *before* gemcitabine. Virtually all previous clinical studies administered both drugs together starting on day 1. This pharmacologic principle provided the rationale for giving capecitabine alone for the first 4 days of the GTX regimen and is further corroborated by our preclinical data. We found the cytotoxicity of gemcitabine with 5-FU was *sub-additive* if both agents were delivered simultaneously and *additive* if the fluoropyrimidine was delivered first by at least 2–4 days before gemcitabine to human pancreatic cancer cell lines [33].

Together, docetaxel, 5-FU and gemcitabine produced synergistic cytotoxicity (4.6-fold) in three human pancreatic cancer cell lines only when 5-FU preceded gemcitabine and docetaxel by at least 2–4 days and only additive cytotoxicity when all three drugs were added simultaneously (Fig. 2). Experiments performed to elucidate the mechanisms of the GTX synergy found GTX increased FAS, caspase 8, Bax and Bak and decreased Bc1-2 up to ninefold but *not* when all three drugs were added simultaneously [7, 8]. Also, GTX specifically inhibited the activation of the anti-apoptotic MEK-ERK segment of the MAP kinase (MAPK) pathway. Thus, GTX is acting similar to a targeted agent in the MEK-ERK pathway (manuscript in preparation). In addition, this GTX-mediated induction of synergistic apoptosis did not occur with either single drugs or doublet combinations of drugs within GTX, or when all three drugs were given simultaneously (Fig. 2) [7, 8]. This correlates with data from Sawada et al. [34] who showed that docetaxel and capecitabine produced synergistic cytotoxicity in a murine in vivo colon cancer model only when given in a specific schedule dependent manner.

The major factor which frequently determines survival in metastatic pancreatic cancer is liver metastases which occurred in 94% of our patients. Overall median survival for all patients was 11.2 months (C.I. 8.1−15.1), but when analyzed for response in metastatic sites (94% liver, 6% lung) the median survival increased (Table 6). Median survival for patients who had a metastatic site response (CR/PR) was 13.5 months (C.I. 9.0–29.5); for MR/SD it was 18.1 months (C.I. 3.7−30.6); and patients with PD in metastatic sites it was 3.9 months (C.I. 2.1−7.5) (Table 6). The prolonged median survival in the MR/SD group (18.1 months) was mostly due to long periods of SD induced by GTX. Though the separation of metastatic site response from overall response rates is not commonly done, we propose that it may be an alternative method of analysis,

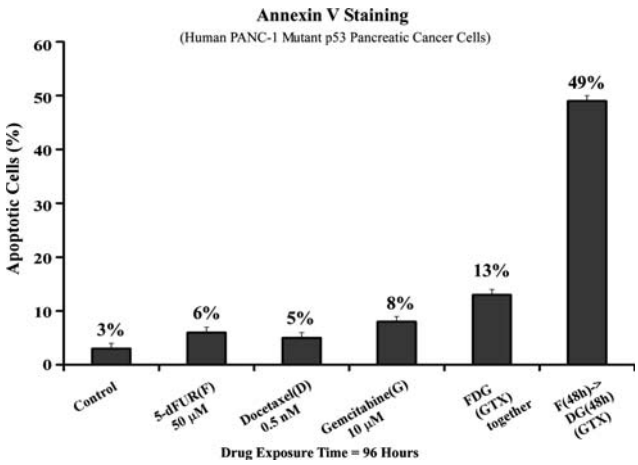

Fig. 2 The In Vitro Cytotoxicity of GTX is Dependent Upon Schedule. The human pancreatic adenocarcinoma cell line PANC-1 was tested in vitro against various schedules of gemcitabine (G) (10 μM), 5-deoxy-fluorouridine (F) (5-dFUR) at 50 μM and docetaxel (D) at 0.5 nM for 96 h. The drug concentrations approximate the in vivo plasma concentrations achieved by the GTX regimen. Floating and adherent cells were pooled, analyzed for extracellular expression of phosphatidylserine as a marker for apoptosis by the Annexin V assay quantitated by flow cytometry. After subtraction of control values, the combination (FDG) showed additive cytotoxicity if all three drugs were delivered together or supra-additive or synergistic cytotoxicity if the 5-dFUR preceded the docetaxel/gemcitabine exposure by 48 h (GTX last bar). Thus, there was a 4.6-fold increase in cytotoxicity by GTX (46% death) compared to the cytotoxicity induced by the summation of the three individual drugs (10% death) or by giving the three drugs in GTX simultaneously (10% death, FDG together)

along with stating overall median survival, in this disease because the primary tumor is highly desmoplastic and may not show any significant decrease though the malignant cell population may have been substantially reduced. Alternatively, the metastatic sites in the liver and lung tend to have less desmoplasia and thus more amenable to visualize tumor shrinkage in scans. This method of analysis demonstrates a good correlation between survival and response in metastatic sites in our patients.

We have published on the efficacy of neoadjuvant GTX in 24 patients with non-metastatic, inoperable pancreatic cancer due to major vessel involvement [35]. Neoadjuvant treatment consisted of 3 cycles of GTX followed by standard conformal radiotherapy (5,040 rads) with weekly low dose gemcitabine (200–250 mg/m²) as a radiosensitizer. Sixteen of the total 24 patients (67%) were judged operable after the neoadjuvant regimen and 81% of operated patients (13 of 16) had negative margins; 56% (9 of 16) had both negative nodes and margins; and 19% (3 of 16) were complete pathologic responders. Only 1 patient (4%) developed metastases during the 20 week neoadjuvant treatment period. Thus, by ITT analysis, 13 of 24 total inoperable patients (54%) underwent a successful Whipple procedure with negative margins [35].

In an interim analysis of our current, prospective phase II study of GTX in 44 patients consecutively accrued to date with good PS (0–2) and untreated metastatic pancreatic cancer (96% liver, 4% lung), the response rate by ITT analysis is at least the same as reported here [33]. The true clinical efficacy of GTX in the treatment of metastatic pancreatic cancer awaits phase III testing against the current standard of care (gemcitabine ± erlotinib) before verification of these preliminary results can be substantiated. Until then, we suggest caution in extrapolating these initial retrospective results to the clinical treatment of metastatic pancreatic cancer.

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References

1. Jemal A, Murray T, Samuels A (2003) Cancer statistics, 2003. CA-Cancer J Clin 53:5–26
2. Burris HA, Moore MJ, Anderson J et al (1997) Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Onc 15(6):2403–2413
3. Brand R, Capadano M, Tempero M (1997) A phase I trial of weekly gemcitabine administered as a prolonged infusion in patients with pancreatic cancer and other solid tumors. Invest New Drugs 15(4):331–341
4. Tempero M, Plunkett W, Ruiz Van Haperen V, Hainsworth J, Hochster H, Lenzi R, Abbruzzese J (2003) Randomized phase II comparison of dose-intense gemcitabine: thirty-minute infusion and fixed dose rate infusion in patients with pancreatic adenocarcinoma. J Clin Onc 21(18):3402–3408
5. Moore M, Goldstein D, Hamm J et al (2005) Erlotinib plus gemcitabine compared to gemcitabine alone in patients with advanced pancreatic cancer. A phase III trial of the National Cancer Institute of Canada Clinical Trials Group [NCIC-CTG]. J Clin Oncol 23:1s, (Suppl, Abstr 1)
6. Cunningham D, Chau I, Stocken D, Barletta E, Moscetti L, Recchia F et al Phase III randomised comparison of gemcitabine (GEM) versus gemcitabine plus capecitabine (GEM-CAP) in patients with advanced pancreatic cancer. Eur J Cancer Suppl 4, Abstr. PS 11
7. Fine RL, Fogelman DR, Sherman W et al (2003) The GTX regimen: A biochemically synergistic combination for advanced pancreatic cancer (PC). Proc Am Soc Clin Onc Abstr #1129
8. Fine RL, Fogelman DR, Schreibman S, Guba S, Sharma J, Shapiro G (2004) GTX chemotherapy for metastatic pancreatic cancer: Response, survival, and toxicity data. J Clin Oncol 22:381s suppl. Abstr #4271
9. Sherman WH, Fine RL (2001) Combination gemcitabine and docetaxel in advanced adenocarcinoma of the pancreas. Oncology 60(4):316–321
10. Hess V, Salzberg M, Borner M et al (2003) Combining capecitabine and gemcitabine in patients with advanced pancreatic carcinoma: A phase I/II trial. J Clin Oncol 21(1):66–68
11. Fogelman DR, Sherman W, Schreibman S, Fine RL (2003) Effective salvage chemotherapy with minimal toxicity for relapsed, advanced pancreatic cancer. Proc Am Soc Clin Onc Abstr #1517
12. Fogelman D, Fine RL, Schreibman S (2004) Effective salvage therapy (T-GX) for pancreatic cancer patients after chemotherapy with GTX. J Clin Oncol 22:380s suppl. Abstr #4268
13. Khorana A, Fine RL (2004) Pancreatic cancer and thromboembolic disease. Lancet Oncol 5(11):655–663
14. Poplin E, Levy D, Berlin J et al (2006) Phase III trial of gemcitabine (30-minute infusion) versus gemcitabine (fixed-dose-rate infusion [FDR]) versus gemcitabine + oxaliplatin(GEMOX) in patients with advanced pancreatic cancer (E6201). J Clin Oncol 24(18):2006, LBA 4004
15. Cartwright TH, Cohn A, Varkey JA et al (2002) Phase II study of oral capecitabine in patients with advanced or metastatic pancreatic cancer. J Clin Oncol 20(1):160–164
16. Stathopoulos GP, Syrigos K, Polyzos A et al (2004) Front-line treatment of inoperable or metastatic pancreatic cancer with gemcitabine and capecitabine: an intergroup, multicenter, phase II study. Ann Oncol 15:224–229
17. Hermann R, Bodoky G, Ruhstaller T et al (2005) Gemcitabine (G) plus capecitabine versus G alone in advanced/metastatic pancreatic cancer. A randomized phase III study of the SAKK and CECOG groups, Proc Am Soc Clin Oncol Abst #4010
18. Rougier P, Adenis A, Dureux M et al (2000) A phase II study: Docetaxel as first line chemotherapy for advanced pancreatic adenocarcinoma. Eur J Cancer 36:1016–1025
19. Androulakis N, Kourousis C, Dimopoulos M (1999) Treatment of pancreatic cancer with docetaxel and granulocyte colony-stimulating factor: a multicenter phase II trial. J Clin Oncol 17:1779–1785
20. Schneider BP, Ganjoo KN, Seitz DE et al (2003) Phase II study of gemcitabine plus docetaxel in advanced pancreatic cancer: a Hoosier Oncology Group study. Oncology 65(3):218–223
21. Louvet C et al (2004) Gemcitabine versus GEMOX (gemcitabine + oxaliplatin) in non resectable pancreatic adenocarcinoma : Final results of the GERCOR /GISCAD Intergroup Phase III. J Clin Oncol 22:315s suppl, abstr #4008
22. Heineman V, Quietzsch D, Gieseler F (2003) A phase III trial comparing gemcitabine plus cisplatin vs. gemcitabine alone in advanced pancreatic carcinoma, Proc Am Soc Clin Oncol Abst #1003
23. Rocha Lima CM, Rotche R, Jeffrey M et al (2003) A randomized phase 3 study comparing efficacy and safety of gemcitabine (GEM) and irinotecan (I), to GEM alone in patients (pts) with locally advanced or metastatic pancreatic cancer who have not received prior systemic therapy. Proc Am Soc Clin Onc Abst #1005
24. Kozuch P, Grossbard ML, Barzdins A et al (2001) Irinotecan Combined with gemcitabine, 5-fluorouracil, leucovorin, and cisplatin (G-FLIP) is an effective and noncrossresistant treatment for chemotherapy refractory pancreatic cancer. Oncologist 6(6):488–495
25. El-Rayes BF, Zalupski MM, Shields AF et al (2003) Phase II study of gemcitabine, cisplatin, and infusional fluorouracil in advanced pancreatic cancer. J Clin Oncol 15(1):2920–2925
26. Araneo M, Bruckner HW, Grossbard ML et al (2003) Biweekly low-dose sequential gemcitabine, 5-fluorouracil, leucovorin and cisplatin (GFP): A highly active novel therapy for metastatic adenocarcinoma of the exocrine pancreas. Cancer Invest 21(4):489–496
27. CALGB News, http://www.calgb.org/index.php?action=fullnews&id = 28; or http://www.calgb.org website
28. Kindler HL, Bylow KA, Hochster HS et al (2006) A randomized phase III study of bevacizumab (B) and gemcitabine (G) plus

cetuximab (C) or erlotinib (E) in patients (pts) with advanced pancreatic cancer (PC): a preliminary analysis. J Clin Onc 24(18S):A4040
29. Berlin JD, Adak S, Vaughn DJ et al (2000) A phase II study of gemcitabine and 5-fluorouracil in metastatic pancreatic cancer: an Eastern Cooperative Oncology Group study (E3296). Oncology 58:215–218
30. Berlin JD, Catalano P, Thomas J et al (2002) Phase III study of gemcitabine with fluorouracil versus gemcitabine alone in patients with advanced pancreatic carcinoma: Eastern Cooperative Oncology Group Trial E2297. J Clin Oncol 20:3270–3275
31. Reiss H, Helm A, Niedergethmann M et al (2005) Randomized, prospective multicenter phase III trial of gemcitabine, 5FU, folinic acid versus gemcitabine alone in patients with advanced pancreatic cancer. Proc Am Soc Clin Oncol Abst #4009
32. Hidalgo M, Castellano D, Paz-Ares L et al (1999) Phase I-II study of gemcitabine and fluorouracil as a continuous infusion in patients with pancreatic cancer. J Clin Oncol 17(2):585–592
33. Fine RL, Fogelman DR, Sherman W et al (2006) Gemcitabine, Docetaxel, and Capecitabine (GTX) in the treatment of metastatic pancreatic cancer (PC): A prospective phase II Study. Proc Am Soc Clin Oncol Abst #14024
34. Sawada N, Ishikawa T, Fukase Y et al (1998) Induction of thymidine phosphorylase activity and enhancement of capecitabine efficacy by taxol/docetaxel in human cancer xenografts. Clin Cancer Res Suppl 4(4):1013–1019
35. Fogelman DR, Chen J, Chabot J, Allendorf J, Schreibman S, Ennis R, Fine RL (2004) The evolution of adjuvant and neoadjuvant chemotherapy and radiation for advanced pancreatic cancer: From 5-FU to GTX. Surg Oncol Clin No Am 13:711–735