

A phase I study of the biomodulation of capecitabine by docetaxel and gemcitabine (mGTX) in previously untreated patients with metastatic adenocarcinoma of the pancreas

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Abstract

Background Pancreas cancer remains a formidable challenge. We report the first prospective analysis of the 3-drug combination of gemcitabine (G), docetaxel (T) and capecitabine (X) (mGTX) with schedule modification to maximize biomodulation of X.

Methods We conducted a dose escalation study of mGTX in first-line treatment of metastatic pancreas cancer using three dose levels (DL 1–3). Patients received docetaxel on days 1 and 8, gemcitabine on days 8 and 15, and capecitabine on days 8 through 21. Gemcitabine dose was fixed at 750 mg/m² over 75 min, capecitabine was given twice daily and escalated from 500 to 650 mg/m² at DL2 and docetaxel increased from 30 to 36 mg/m² at DL3.

Results Twenty-one patients (18 evaluable) were enrolled in the study. MTD was reached at DL3 and one DLT was observed at DL2 (prolonged neutropenia). The most common grade 3/4 toxicities were leukopenia (29%) and

neutropenia (29%) and fatigue (25%). Tumor growth control rate was 80% (11% PR; 69% SD lasting at least 3 months). Median progression-free-survival was 5.8 months (95% CI 2.7, 10.6) and median overall survival was 7.4 months (95% CI 3.8 16.8). CA 19-9 decreased by at least 50% from baseline in half the patients.

Conclusion mGTX demonstrates acceptable tolerability with interesting activity in patients with pancreatic cancer. The recommended doses for phase II studies are docetaxel 36 mg/m² days 1 and 8, gemcitabine 750 mg/m² over 75 min days 8 and 15, and capecitabine 625 mg/m² twice daily days 8 through 21.

Keywords Pancreas · Adenocarcinoma · Gemcitabine · Capecitabine · Docetaxel

Introduction

Pancreatic cancer is the fourth leading cause of cancer death in the United States. It is estimated that 42,470 Americans will develop pancreatic cancer in 2009 and 35,240 will die from this disease [1]. The 5-year survival for pancreas cancer has not significantly improved over the past four decades [1]. For many years, 5-FU was the mainstay of treatment. In 1997, a randomized phase III trial demonstrated gemcitabine to be superior to 5-FU establishing it as the new standard for advanced pancreas cancer [2]. More recently, the addition of erlotinib to gemcitabine has been shown to provide a modest survival advantage over gemcitabine alone [3]. Ongoing efforts to improve on the activity of gemcitabine have been undertaken, mostly without success [4, 5].

Docetaxel has demonstrated activity both as a single agent and in combination with other agents including

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gemcitabine in patients with advanced pancreas cancer [6, 7]. Capecitabine, an oral fluoropyrimidine, has also shown single agent activity in the first line treatment of metastatic pancreas cancer [8]. In a recent randomized phase III study, gemcitabine in combination with capecitabine has shown a trend towards improving survival when compared to gemcitabine [9].

In a retrospective analysis, the combination of gemcitabine, docetaxel and capecitabine (GTX) has shown significant activity and a favorable toxicity profile in pancreas cancer patients [10]. GTX has subsequently been adopted by multiple practices in the US, despite the lack of prospective validation of its efficacy or safety profile. We decided to prospectively evaluate the combination of all three agents—gemcitabine, docetaxel and capecitabine—in patients with advanced pancreas cancer. Unlike the published schedule of GTX, our proposed schedule was aimed at biomodulating the activity of capecitabine by both docetaxel and gemcitabine.

Our pharmacobiologically-based scheduling had the following rationale: (a) docetaxel induces thymidine phosphorylase (TP)—the main activating enzyme of capecitabine—with maximal activity noted at 4–6 days, and persisting for at least 10 days after exposure to docetaxel [11]. In this study, capecitabine is initiated on day 8, following the first dose of docetaxel (Fig. 1). Similar pharmacobiologic-based scheduling using the combination of docetaxel and capecitabine was previously shown by our group to have activity in a phase I study in solid tumors and was both safe and effective in a phase II study in lung cancer [12, 13] (b) gemcitabine inhibits ribonucleotide reductase resulting in enhanced binding of 5-FU to thymidylate synthase and subsequent higher incorporation into DNA [14]. Enhanced effects have been demonstrated with the drugs given sequentially, a prolonged-infusion gemcitabine given first, followed by 5FU for at least 24 h [14]. This rational combination has shown promising clinical activity in refractory colon cancer and other tumor types, including pancreas cancer [10–12]. In this study, we chose to administer gemcitabine by fixed dose rate infusion (10 mg/m²/min) as previously published [15], on weeks 2 and 3 along with concurrent capecitabine (Fig. 1).

The primary objective of this study was to identify the maximum tolerated dose (MTD) of the combination of capecitabine, docetaxel, and gemcitabine (mGTX) in patients with previously untreated metastatic adenocarcinoma of the pancreas. Secondary objectives were to define the qualitative and quantitative toxicities of the combination in regard to organ specificity, time course, predictability, and reversibility, and to document the preliminary efficacy of the combination in patients with pancreas cancer.

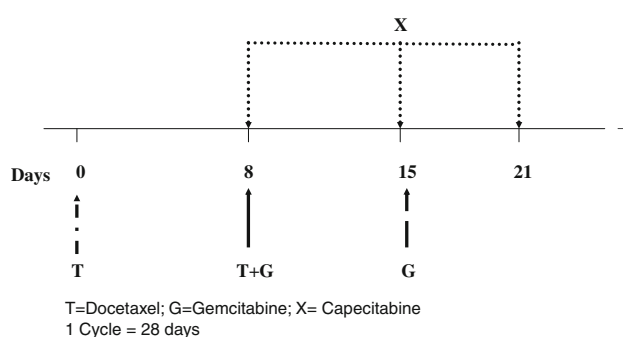


Fig. 1 Schema of mGTX

Patient and methods

This was an NCCN sponsored phase I study to define the MTD of mGTX. The study was registered with PDQ/ClinicalTrials.gov (registration number NCT00320749). The study was conducted at the Ohio State University (lead) and the University of Michigan (subsite). This study was approved by both The Ohio State University and the University of Michigan Institutional Review Board. The study was monitored by the Bridgesite Research Site Management Organization. Capecitabine (Xeloda®) was provided by Roche Pharmaceuticals through NCCN. Gemcitabine (Gemzar®) and Docetaxel (Taxotere®) were purchased commercially.

Eligibility

Patients were required to have histologically or cytologically confirmed metastatic pancreatic adenocarcinoma and measurable disease per RECIST criteria [16]. No prior chemotherapy or radiation therapy was allowed within the previous 5 years unless it was given as adjuvant treatment for pancreas cancer, in which case 4 weeks had to have elapsed from the end of the prior treatment to the beginning of this study. Patients were required to have an ECOG performance status of 0 or 1, as well as a life expectancy of at least 12 weeks. Additional eligibility criteria included adequate organ function, defined as follows: absolute neutrophil count (ANC) greater than 1,500/mm³; hemoglobin > 9 g/dL; platelet count ≥ 100,000/mm³; creatinine <1.5 upper limit normal (ULN); serum bilirubin ≤ ULN; AST/ALT < 1.5 ULN. Patients were to have no evidence of any active infection, and they were to be free of other malignancies for ≥ 5 years (except basal and squamous cell skin cancers and carcinoma in situ of the cervix). Any preexisting peripheral neuropathy was required to be ≤ grade 1, as defined by the NCI Common Toxicity Criteria version 3.0. Exclusion criteria included the following: Age less than 18 years and pregnant

or lactating women; psychiatric disorders that would interfere with consent or follow-up; uncontrolled diabetes mellitus, defined as random blood sugar of > 250 mg/dL; patients with a history of myocardial infarction within the previous 6 months, congestive heart failure requiring therapy, or unstable angina; patients being anticoagulated with coumadin-based medications; and patients with a known history of severe hypersensitivity reaction to either docetaxel, gemcitabine, or capecitabine. All women of childbearing capacity were required to have a negative pregnancy test prior to study entry, and both men and women of childbearing capacity were required to utilize an effective contraceptive method while on the study and for 3 months thereafter, if applicable.

Treatment plan (Fig. 1)

Treatment was administered on an outpatient basis. The study consisted of the following schedule: Docetaxel (T) on days 1 and 8, gemcitabine (G) at a fixed dose rate on days 8 and 15 and capecitabine (X) on days 8–21. The first dose of X on days 8 and 15 was given after G infusion was completed. This was followed by 1 week of rest. Three dose levels were planned as detailed in Table 1. A standard 3 + 3 dose escalation scheme was used. Three patients were initially entered at Dose level 1. In the absence of a pre-specified dose-limiting toxicity (DLT) in any of these three patients, the next three patients were entered at Dose level 2. The same principle was exercised for escalation to dose level 3. At any given dose level, if 1 of 3 patients had a DLT, an additional 3 patients were entered at that dose level. If more than 1 of 3 patients experienced a DLT, the MTD has been exceeded. Dose de-escalation would occur. The maximum tolerated dose (MTD) was the highest dose level at which 3 of 3 or 5 of 6 patients tolerated the dose without DLT. When MTD is determined, 6 additional patients were to be enrolled at this level to better define toxicity and efficacy.

Dosage and dose escalation (Table 1)

The dosage and dose escalation schemata are detailed in Table 1. Essentially, docetaxel was given as a 30-min IV infusion, with oral administration of dexamethasone 12 h prior, immediately prior to, and 12 h after, infusion of docetaxel. Loperamide was used as treatment but not for prophylaxis of diarrhea. Gemcitabine was administered intravenously over 75 min at a fixed-dose rate. Capecitabine was given orally, twice daily.

Dose modifications

Separate criteria for dose reductions were followed for docetaxel, gemcitabine, and capecitabine, depending upon

Table 1 Dose escalation schema

	Schedule/dose level (mg/m ²) ^a	No. of patients	No. with DLTs	Best responses
1	D 30 C 1,000 G 750	3	0	1PR/2SD
2	D 30 C 1,250 G 750	8 ^b	1	3SD/3PD/2NE
3	D 36 C 1250 G 750	4 ^c + 6 ^d	0	1PR/8SD/1NE

^a (D)ocetaxel i.v. over 30 min on days 1 and 8; (C)apecitabine p.o. in split doses bid on days 8–21 (G)emcitabine i.v. over 75 min on days 8 and 15

^b 2 patients were non-evaluable for DLT or response

^c 1 patient was non-evaluable for DLT or response

^d 6 patients were enrolled at the MTD to further define toxicities and preliminary activity

the type of toxicity observed and whether it was observed within a treatment cycle or at the beginning of a subsequent treatment cycle. Dose adjustments during a course of therapy were based on toxicity observed the day of treatment. All dose adjustments were relative to the dose given at a previous week of that cycle. If multiple toxicities were seen, the dose administered was based upon the most severe toxicity experienced. In general, grade 3 and 4 hematologic toxicities required dose omissions for all three drugs, with resumption at the original dose occurred within a course when the toxicity had resolved to $\leq$ grade 2. Dose modifications of capecitabine were based on the total daily dose administered. Capecitabine treatment interruptions were considered to be lost treatment days and missed doses were not to be replaced and the planned treatment schedule was maintained.

A new course of treatment was reinitiated when the granulocyte count was $\geq 1,500/\text{mm}^3$ and the platelet count was $\geq 100,000/\text{mm}^3$ and any other treatment-related toxicities were $\leq$ grade 1; otherwise treatment was temporarily withheld and the patient reevaluated 1 week later. If toxicities were not resolved to $\leq$ grade 1 after a 2-week delay, then the patient was removed from therapy, unless clinical benefit had been documented in which case an extra week delay was allowed.

Evaluation

Radiological assessment was done every 8 weeks and responses were measured according to the RECIST criteria [16]. This study utilized the CTC version 3.0 for toxicity (http://ctep.info.nih.gov/CTC3/ctc_ind_term.htm).

Dose-limiting toxicity (DLT) was determined in the first 2 cycles of therapy and defined as follows: any grade 4 neutropenia lasting more than 5 days or accompanied by $\geq$ grade 2 fever, or any grade 4 thrombocytopenia; grade 3 or 4 non-hematologic toxicity that results in interruption of capecitabine for more than 5 days; and clinical inability (due to toxicity) to start the next cycle of treatment within 2 weeks of planned start date. The aforementioned toxicities needed to be considered drug related by the investigator to be considered DLT. Qualifying toxicities deemed definitely not related to the study drugs were not counted as DLTs. Prophylactic use of colony-stimulating factors or erythropoietin was not permitted in the first 2 cycles to allow a better definition of DLTs.

Results

Demographics (Table 2)

A total of 21 patients were enrolled into the study between December 2005 and February 2008. The demographics of the patients are summarized in Table 2. The median age was 59, and 81% of the patients had a performance status of 1. A total of 86 cycles were administered, with a median of 4 cycles per patient (range, 1–8 cycles). The median duration of treatment was 4.1 months.

Adverse events and DLTs (Tables 1, 3)

Three patients were enrolled at treatment-dose level 1, eight at dose-level 2 and ten at level 3 (Table 1). We observed

Table 2 Patient characteristics

Characteristic	Number of patients
Total number of patients	21
Mean age (range) in years	59 (48–72)
Sex	
Women	13
Men	8
ECOG performance status	
0	4
1	17
Prior adjuvant treatment	
None	18
Gemcitabine and/or 5FU	3
Radiation	2
Metastatic sites	
Liver only	8
Liver + other	5
Other	8

Table 3 Common toxicities ($N = 21$ -throughout all cycles)

	Percentage of all grades	Percentage of grade 1/2	Percentage of grade 3/4
Hematologic			
Leukopenia	67	38	29
Neutropenia	53	24	29
Anemia	48	48	0
Thrombocytopenia	48	48	0
Non-hematologic			
Fatigue	85	60	25
Nausea	75	75	0
Diarrhea	75	65	10
Alopecia	60	60	0
Neuropathy	50	50	0
Vomiting	40	35	5
Mucositis	35	30	5
Transaminitis	25	25	0

only 1 DLT throughout the study at dose level 2 (prolonged neutropenia). Three patients were not evaluable for DLT (2 on dose level 2 and 1 on dose level 3) as they withdrew consent after one cycle of therapy for reasons unrelated to toxicity, (requested treatment closer to home (2 patients) or decided to pursue “natural remedies” (1 patient)). All patients were evaluable for toxicity (Table 3). The most commonly-experienced grade 3 or 4 toxicity was neutropenia (29%). The most common toxicities of any grade were fatigue (85%) followed by nausea (75%) and diarrhea (75%). Severe fatigue occurred in 25% and grade 3 diarrhea in 10% as therapy continued beyond cycle 2. One patient experienced grade 3 hand-foot syndrome (HFS) after cycle 2. One patient did require dose reductions during the first cycle of therapy, and 33% of all patients required a dose reduction during their course of treatment. Reasons for withdrawal from the study included progressive disease (10), toxicity (3), request for treatment holiday after at least 5 cycles on therapy (3), request for treatment closer to home (2), patient choice (1) and clinical deterioration (1).

Anti-tumor activity (Tables 1, 4)

Clinical activity is described in Table 4. Three patients were non-evaluable for response or progression free survival as they withdrew consent after 1 cycle only. All patients were evaluable for overall survival. Two patients had a confirmed partial response (PR) at dose levels 1 and 3 (Table 1). The tumor growth control rate (TGCR) is 80% (11% PR; 69% of SD lasting over 3 months). Median progression-free survival (mPFS) is 5.8 months. Median overall survival (mOS) is 7.4 months and the one-year survival rate is 33%. CA19-9 was elevated at baseline in 18 patients and decreased by at

Table 4 Efficacy results

Response rate (%)	11
Complete	0
Partial	11
95% CI	1.4, 34.7
Stable disease	72
SD $\geq$ 3 months	69
TGCR ^a (%)	80
95% CI	58.6, 96.4
One-year survival (%)	33
Decrease in CA19-9 by > 50% baseline (%)	50
Progression-free-survival (months)	
Median	5.8
Range	0.2–10.6
95% CI	2.7, 10.6
Overall survival (months)	
Median	7.4
Range	0.2–24.2
95% CI	3.8 16.8

There were 18 patients (out of a total of 21) that are evaluable for response or Ca 19-9 response. All 21 patients were evaluable for survival
 TGCR^a = Tumor Growth Control Rate = (ORR + SD) $\geq$ 3 months

least 50% from baseline in half of those patients on therapy. All patients have expired except for one patient who is living 34 months from the first day of study treatment.

Discussion

Pancreas cancer remains resistant to therapy with very little progress made over the last few decades. Capecitabine, docetaxel and gemcitabine have each shown evidence of activity in advanced pancreas cancer [6–9, 17, 18]. Initial support for combining all three drugs was based on evidence of clinical activity for a combination known as GTX, with a schedule that is different from the one described in this study (mGTX). As published, GTX consisted of X at 750 mg/m² PO bid on days 1–14, G at 750 mg/m² over 75 min and T at 30 mg/m² on days 4 and 11 for a 21 day cycle. In a retrospective analysis of 35 patients with pancreas cancer treated with GTX, 29% of patients had a response (using WHO criteria) and 31% had a minor response or stable disease, with a reported median progression-free survival (in responders only) of 6.3 months and median overall survival of 11.2 months [10].

The basis for the pharmacobiologic schedule with mGTX is supported by preclinical and clinical data. Docetaxel has been shown to induce TP in a time dependent and transient manner [11–14]. Gemcitabine inhibits ribonucleotide reductase (RR) resulting in enhanced binding of 5-fluorodeoxyuridine-monophosphate to thymidylate synthase

with greater effects seen when the drugs were given sequentially, with a prolonged-infusion gemcitabine given first [14]. With the coincident timing of TP activation and RR inhibition, we aimed at maximizing the potentiation of capecitabine. As such, capecitabine was given on days 8–21 to maximize its potential activation by docetaxel—given on days 1 and 8- and by gemcitabine -given on days 8 and 15- for a 28-days cycle Fig. 1). This study is the first prospective analysis of the triple drug combination in patients with metastatic pancreatic cancer.

In our study, mGTX was found to be relatively safe and tolerable with only one dose limiting toxicity noted at dose level 2 (prolonged neutropenia). We have reached our MTD with no significant DLTs. The choice for the maximal doses selected (at DL3) were based on previous safety and efficacy published data [10, 13]. The most common grade 3 and 4 toxicities were leukopenia, neutropenia, fatigue, and diarrhea. These toxicities were present at all dose levels. Very few patients experienced hand-foot syndrome of any grade most likely because of the lower dose of capecitabine used on this study. Half of the patients withdrew from the study for reasons other than progression. Although it is beyond the scope of a phase I study to assess efficacy, this was a disease specific study in patients who were previously untreated. Patients with partial responses or a meaningful (prolonged) stable disease were seen at all dose levels. There was evidence of interesting activity on this study with 80% of all patients enrolled achieving disease control status (PR or SD lasting at least 3 months). The median progression free survival of 5.8 months compares favorably to historical controls, including GTX. Consistent with the preliminary evidence of activity is a biochemical response in half of the patients, with elevated CA19-9 experiencing a drop of 50% or more of their baseline levels on treatment. Previous studies have suggested that a drop in CA19-9 levels of at least 25% from baseline is predictive of an improved outcome [19]. Additionally, the median overall survival of 7.4 months is promising for a population of patients with metastatic pancreas cancer when compared to the historical controls of gemcitabine with or without erlotinib (studies that included patients with both locally advanced and metastatic disease) [2, 3].

There are a number of elements that limit the interpretation of our results, including potential selection bias and the small number of patients. Another limitation of our study includes the absence of accompanying correlative studies to validate the presumed biomodulation of capecitabine. Unfortunately, in pancreas cancer as in most solid tumors, such pharmacodynamic studies tend to be very challenging in terms of logistics, cost and eventual interpretation, and therefore, not justifiable. Nonetheless, the clinical results provided by our study suggest a promise of activity with acceptable tolerability.

Should we continue to explore the role of the combination of gemcitabine, docetaxel and capecitabine in this disease? The triple combination has been widely adopted despite the lack of valid prospective data. Our phase I study of mGTX suggests benefits similar to the historical benefits to GTX. However, there is a significant burden to justify further exploration of the combination of all three drugs given the fact that the combination has shown only modest improvement in efficacy over the historical controls of single agent gemcitabine with or without erlotinib. A potential avenue for further exploration is in the neoadjuvant setting, especially in patients with borderline resectable and/or locally advanced disease. The response rate in advanced disease was unimpressive; however, in an earlier stage it may provide more benefit in the above-mentioned patient group. A retrospective analysis of GTX in what was described as a neoadjuvant treatment of “unresectable” disease reported a high rate of resectability [20]. The retrospective nature of this report and the definition of unresectable disease render the utility of the treatment uncertain [21].

In conclusion, mGTX was found to be safe with evidence of interesting preliminary activity. The recommended doses for phase II studies using this schedule are docetaxel 36 mg/m² on days 1 and 8, gemcitabine 750 mg/m² over 75 min days 8 and 15, and capecitabine 625 mg/m² days 8 through 21. As widely suggested, further research and development in pancreas cancer should continue on exploring the role of novel biologic agents with promising targets such as RAS-MAPK, PI3K-AKT-mTOR, and hedgehog signaling pathways [22, 23].

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Conflict of interest statement Tanios Bekaii-Saab has received Research Grants from Sanofi-Aventis and Roche, is on the speaker bureau for Sanofi-Aventis and Lilly and has received honoraria from Sanofi-Aventis and Lilly. Other Co-Authors have no declared conflict of interest.

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