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ORIGINAL ARTICLE

Docetaxel plus gemcitabine in combination with capecitabine as treatment for inoperable pancreatic cancer: a phase II study

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Abstract
Purpose To evaluate the activity and tolerance of gemcitabine in combination with docetaxel and capecitabine in previously untreated patients with advanced pancreatic cancer.
Patients and methods Chemotherapy-naïve patients with locally advanced or metastatic pancreatic cancer were treated with gemcitabine (1,500 mg/m^2 on days 1 and 15), docetaxel (50 mg/m^2 on days 1 and 15) and capecitabine (2,250 mg/m^2, orally in two daily divided doses, on days 1–7 and 15–21). All three drugs were administered in 4-week cycles, in an initial prospective plan of six cycles. The primary end-point was response rate.
Results Forty patients were enrolled in the study. At the time of enrollment, 40% of patients had locally advanced and 60% metastatic disease. All patients were evaluable for response and toxicity. On an intent-to-treat analysis, the overall response and disease control rates were 40 and 80%, respectively. The median progression-free survival was 6.0 months, and the median overall survival was 9.0 months. Major grade 3/4 toxicities were neutropenia (17.5%), diarrhea (10%) and hand-foot syndrome (7.5%). There was no treatment-related death.
Conclusion The combination of gemcitabine with docetaxel and capecitabine is feasible and exhibits satisfactory degree of activity in patients with advanced pancreatic cancer, deserving further exploration.

Keywords Docetaxel · Gemcitabine · Capecitabine · Pancreatic cancer · Phase II

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Introduction

In spite of important advances in recent years in the understanding of the molecular biology of pancreatic cancer, minimal progress has been made in the treatment of patients with locally advanced and metastatic disease. Although, chemotherapy, compared with best supportive care, has been shown to improve both survival and quality of life [1], therapeutic results of the current standard treatment remain disappointing and require urgent improvement.

For more than a decade, gemcitabine is the treatment of choice in patients with advanced pancreatic cancer, as it has been established that provides a clinical benefit and modest survival advantage over treatment with bolus 5-fluorouracil (5-FU) [2]. A number of other agents with diverse mechanisms of action, such as cisplatin, oxaliplatin, irinotecan, 5-FU, capecitabine, docetaxel and erlotinib, have been tested in combination with gemcitabine to improve clinical outcome of patients with advanced disease. A recent large meta-analysis that evaluated 4,465 patients from 15 randomized

trials reported a significant survival advantage associated with gemcitabine combination therapy as compared with gemcitabine alone, especially in patients with a good baseline performance status [3]. More recently, impressive results were reported in a randomized 342 patient trial, using a combination of 5-FU with oxaliplatin and irinotecan (FOLFIRINOX). In this trial, a substantial improvement in survival was shown in patients with metastatic pancreatic cancer [4].

Promising results have been published in a randomized study in 533 patients with advanced pancreatic cancer, as was found that progression-free survival and objective response rates were significantly improved in patients receiving gemcitabine plus capecitabine when compared with gemcitabine alone, although the improvement in overall survival for the combination arm did not reach statistical significance [5]. Similarly, another smaller phase III trial using this combination showed that although a survival advantage was not demonstrated for overall study population, it significantly increased overall survival in the subgroup of patients with good performance status [6].

Docetaxel is another agent that has demonstrated activity in patients with advanced pancreatic cancer, either as monotherapy as well as in combination with other chemotherapy agents, including gemcitabine [7]. In a recent randomized phase II study, contacted by CALGB, combinations of gemcitabine with cisplatin, docetaxel or irinotecan showed similar antitumor activity in metastatic pancreatic cancer [8]. Interesting results were presented in the 2007 ASCO Annual Meeting regarding the combination of docetaxel plus capecitabine in pre-treated patients with advanced adenocarcinoma of the pancreas. Although, the reported response rate was low (12.5%), a clinical benefit was observed in the majority of patients (70.8%) [9].

The feasibility of a triple-drug combination using the aforementioned cytotoxic agents has been investigated in a recently published phase I study [10]. Additionally, promising activity has been reported in two retrospective reviews examining this combination in patients with advanced pancreatic cancer as first-line chemotherapy [11, 12], as well as in a prospective phase II study [13]. Furthermore, the same triple-drug regimen was proven to be quite effective, as second-line treatment, after failure of initial chemotherapy with gemcitabine in patients with metastatic pancreatic cancer [14]. In that study, 35% of patients experienced disease stabilization along with a median survival of 9.5 months.

Based on these data, we performed a prospective phase II study in order to further evaluate the combination of these three agents, in chemotherapy-naïve patients with locally advanced or metastatic pancreatic cancer. The doses and schedule employed in our study were adopted from a previous phase I study in patients with advanced solid tumors conducted by our center [15]; half of the enrolled population had pancreatic cancer. In that study, the major dose-limiting toxicities that observed were grade 4 neutropenia, grade 3 stomatitis and grade 3 diarrhea; all were easily manageable. In addition, a remarkable activity was noticed in a considerable proportion of the study population.

Patients and methods

Patient eligibility criteria

Eligible patients for this study were required to have cytologic or histologic proof of locally advanced or metastatic adenocarcinoma of the pancreas. Other eligibility criteria included measurable disease, age between 18 and 75 years, Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less and a life expectancy >12 weeks. Participants were required to have adequate hematologic function, normal renal function (serum creatinine <1.5 times the institutional upper normal limit [ULN]) and sufficient liver function (defined as bilirubin levels <1.5 × ULN, alkaline phosphatase <2.5 × ULN and aspartate and alanine aminotransferase <2.5 × UNL or <5 × ULN for patients with liver metastasis).

Patients with severe cachexia or malnutrition (20% or more loss of body weight in last 3 months), active uncontrolled infection, symptomatic central nervous system metastasis, psychiatric disorder or myocardial infarction within the last 12 months were not eligible. Patients were also excluded from the study if they had a second primary tumor other than skin squamous cell carcinoma or in situ cervical carcinoma. All patients had to sign a study-specific consent form, and the study was approved by the Ethical and Scientific Committee of our institution.

Treatment plan and dose modifications

Gemcitabine (Gemzar; Eli Lilly, Indianapolis, IN) was administered as a 30-min intravenous infusion at a dosage of 1,500 mg/m^2 on days 1 and 15. Docetaxel (Taxotere; Sanofi-Aventis, Bridgewater, NJ, USA) was given as 1-h intravenous infusion at a dose of 50 mg/m^2 on days 1 and 15, following pre-medication with dexamethasone 8 mg twice daily for a total of 3 days, and capecitabine (Xeloda; Roche, Zurich, Switzerland) was administered orally on days 1–7 and 15–21 at a dose of 2,250 mg/m^2, as two daily divided doses. All patients received anti-emetic therapy consisting of an intravenous 5-HT3 antagonist. The chemotherapy regimen (GTX) was continued for a total of 6 cycles. Treatment was interrupted at any evidence of disease progression, unacceptable toxicity or patient's refusal to continue further treatment.

Minimum requirements for chemotherapy administration were an absolute neutrophil count >1,500/mm^3, platelets count >100,000/mm^3, and no grade 2 or higher non-hematologic toxicity. In case of grade 3/4 or febrile neutropenia, granulocyte-colony-stimulating factor (rhG-CSF) was administered on days 8–12 and 22–26 after chemotherapy. If febrile or grade 3/4 neutropenia occurred, despite rhG-CSF administration, all three drug doses were reduced to 75% of the initial dose. A similar reduction was done in case of thrombocytopenia grade 3 or 4. Drug-specific dose modifications were instituted for any grade 3/4 non-hematologic toxicity (with the exception of alopecia, nausea or vomiting and anemia), depending upon the type of the observed toxicity. More specifically, in case of grade 3/4 hand-foot syndrome, mucositis, diarrhea (capecitabine), fluid retention, fatigue (docetaxel) or hepatic toxicity (gemcitabine), treatment was held until resolution of the toxicity and then resumed at 75% of the previous dose of responsible drug.

Baseline and follow-up evaluation

The baseline assessment had to be performed within 2 weeks before study entry and included a complete medical history and physical examination, complete blood cell count (CBC) with differential and platelet count, biochemistry test and computed tomography (CT) scans of the chest and the abdomen. Whole body bone scan was performed, if clinically indicated. During treatment, a limited history taking, physical examination, complete blood cell count with differentials, blood chemistry and assessment of toxicity were performed before each chemotherapy administration. Toxicity was evaluated according to the National Cancer Institute-Common Toxicity Criteria (version 2.0) [16]. Radiological assessment of response was performed by CT scans every 12 weeks or earlier if clinically indicated, using the Response Evaluation Criteria in Solid Tumors (RECIST 1.0) [17]. All patients who received at least 2 chemotherapy cycles were assessable for response, and all patients who received at least 1 cycle of chemotherapy were considered evaluable for toxicity.

End-points and statistics

The primary end-point of the study was the efficacy of the regimen in terms of objective response rate in the intent-to-treat population. According to Simon's two-stage optimal design [18], assuming that the expected overall response rate will be at least 40% and the minimum acceptable response rate 21%, a sample of 14 patients will be required in the first step. If a minimum of 4 responses is observed, an additional 26 patients would be accrued onto the second stage of the study. Thereby, if at least 12 responses occur among all 40 evaluable patients, the treatment will be declared sufficiently promising. The probability of accepting a treatment with a real response rate of $\leq$20% will be 5%. Conversely, the risk of rejecting a treatment (at the second stage) with a response rate of at least 40% will be 10%.

Secondary end-points were the progression-free survival, the overall survival and the safety of the chemotherapy regimen. Progression-free survival was measured from the date of study entry to the date of the first evidence of disease progression, the date of death (without progression) or the date of last follow-up. Overall survival was measured from the date of study entry to the date of death or last contact. Survival curves were estimated using the Kaplan–Meier method and life tables. Safety analysis was carried out on the treated population using contingency tables and descriptive statistics.

Results

Patients' characteristics

Between May 2005 and October 2009, 40 patients with unresectable pancreatic cancer were enrolled in the study; the patient characteristics are listed in Table 1. Most of the patients were men (65%), and the majority of them had an ECOG performance status 0–1 (92.5%). At the time of enrollment, 16 (40%) patients had locally advanced disease and 24 (60%) had metastatic disease and 11 (27.5%) of them had more than two organs involved.

Dose intensity

A total of 177 treatment cycles were administered (median 5; range 2–6). Thirty-five (87.5%) patients received three or more cycles of chemotherapy. Fourteen (35%) patients received 6 cycles and completed treatment as per protocol. Two (5%) patients discontinued treatment due to toxicity (hand-foot syndrome grade 3). Twenty (50%) patients discontinued treatment due to disease progression, and 4 additional patients (10%) refused further therapy. Seventeen (42.5%) patients received the treatment without dose reductions or delays, whereas in 23 (57.5%), patient's dose reductions and/or treatment delays were required. Fourteen (8%) chemotherapy cycles were delayed (9 for 1 week and 5 for 2 weeks) due to hematologic (8 cycles) and non-hematologic (6 cycles) toxicities. Dose reduction during treatment was required in 15 (37.5%) patients due to hematologic (6 patients) and non-hematologic (9 patients) toxicities. The median delivered dose intensity for docetaxel was 24 mg/m^2/week, for gemcitabine 720 mg/m^2/week and for capecitabine 7,323 mg/m^2/week (96, 96 and 93% of the protocol planned dose, respectively).

Table 1 Patient characteristics

	n	%
Number of patients	40	
Age, years		
Median	64	
Range	27–75	
Sex		
Male	26	65
Female	14	35
Performance status		
0	9	22.5
1	28	70
2	3	7.5
Disease stage		
Locally advanced	16	40
Metastatic	24	60
Number of sites involved		
1	9	22.5
2	20	50
3	10	25
4	1	2.5
Disease localization		
Pancreas	40	100
Lymph nodes	16	40
Liver	22	55
Peritoneum	4	10
Lung	1	2.5

Treatment efficacy

All patients were evaluated for response in the context of an intention-to-treat analysis (Table 2). Five patients received <2 treatment cycles and were included as non-responders, in the response analysis. In two (5%) patients, a complete response (CR) of the disease was achieved. The first patient had locally advanced disease and 7 months after the end of treatment is still without evidence of disease relapse. The second patient relapsed at the completion of chemotherapy. Fourteen (35%; 95% CI: 20.2–49.8%) patients showed partial response (PR) and 16 (40%) disease stabilization (SD). Eight (20%) patients had evidence of disease progression at the first radiological assessment. The overall response rate (ORR) and disease control rates (DCR; CR + PR + SD) were 40% (95% CI: 24.9–55.1%) and 80% (95% CI: 67.6–92.4%), respectively. There was a slight, but not statistically significant differentiation in response rate according to stage of the disease. Of 16 patients with locally advanced disease, one (6.3%) showed CR, 7 (43.8%) PR, 5 (31.3%) SD and 3 (18.8%) progression of disease. Respectively, of 24 patients with metastatic pancreatic cancer, one (4.2%) showed CR, 7 (29.2%) PR, 11 (45.8%) SD and 5 (20.8%) PD (Table 2). Although, the ORR was higher in patient with stage III than in patients with stage IV disease, (50.1 and 33.4%, respectively), this difference was not statistically significant ($P = 0.339$). Moreover, there was no difference in terms of DCR according to disease stage (81.4 and 79.2% for stages III and IV, respectively; $P = 0.754$). The median duration of remission for the responders was 3 months (range, 1–10+) and that for patients with stable disease was 2 months (range, 1–3+).

Table 2 Response to treatment (intention to treat)

	All patients (*n* = 40)	Stage III (*n* = 16)	Stage IV (*n* = 24)
	n (%)	*n* (%)	*n* (%)
Complete response (CR)	2 (5)	1 (6.3)	1 (4.2)
Partial response (PR)	14 (35)	7 (43.8)	7 (29.2)
Overall response rate (ORR; CR + PR)	40%	50.1%	33.4%
Stable disease (SD)	16 (40)	5 (31.3)	11 (45.8)
Disease control rate (DCR; CR + PR + SD)	80%	81.4	79.2%
Progression of disease (PD)	8 (20)	3 (18.8)	5 (20.8)

After a median follow-up period of 8.5 months (range, 3–23), 35 (87.5%) patients experienced disease progression. The median progression-free survival (PFS) was 6.0 months (95% CI: 5.5–6.5 months), and the estimated 6-month and 1-year PFS rate was 62.5 and 14%, respectively (Fig. 1).Twenty-six (65%) patients died due to disease progression during the follow-up period. The median overall survival (OS) was 9.0 months (95% CI: 7.6–10.4 months). The estimated 1-year OS was 38.4% (Fig. 2). There was no difference in PFS according to disease stage, as the median PFS was 6 months, both for stages III and IV disease (Fig. 3). Regarding OS, although the median OS was higher in patient with stage III than in patients with stage IV disease (13 months vs. 8 months, respectively), this difference was not statistically significant (Fig. 4; $P = 0.106$).

Toxicity

All treated patients were assessed for toxicity. There were no treatment-related deaths. Regarding hematologic toxicity, 7 (17.5%) patients developed grade 3 neutropenia; this toxicity was complicated with fever in only one patient (2.5%). One patient developed grade 3 thrombocytopenia without clinical evidence of bleeding. As for non-hematologic toxicity, grade 3 diarrhea (7.5%), grade 3 hand-foot syndrome (7.5%) and onycholysis (5%) were the major toxicities noticed. Only one patient (2.5%) developed grade 4 diarrhea requiring hospitalization. All other toxicities were

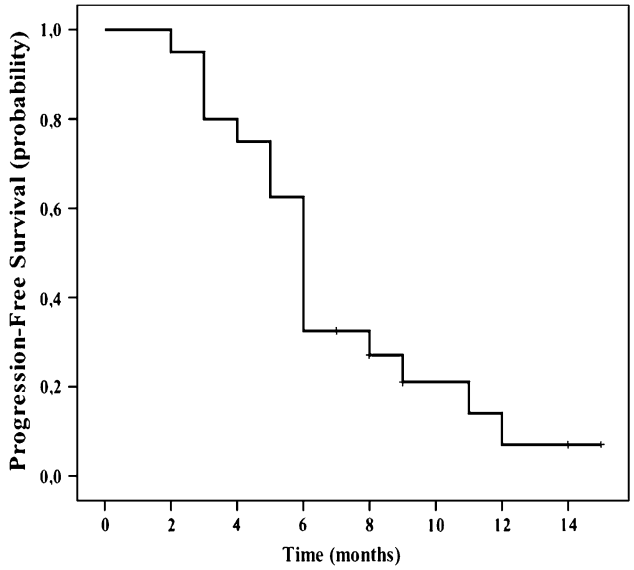

Fig. 1 Kaplan–Meier progression-free survival curve of patients treated with gemcitabine, docetaxel and capecitabine

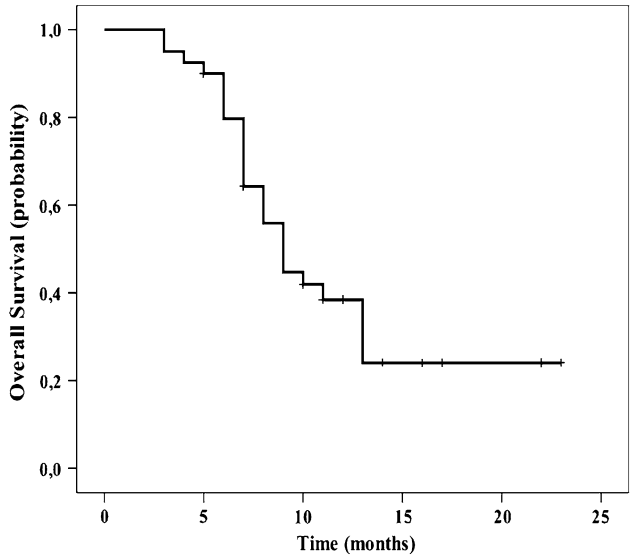

Fig. 2 Kaplan–Meier overall survival curve of patients treated with gemcitabine, docetaxel and capecitabine

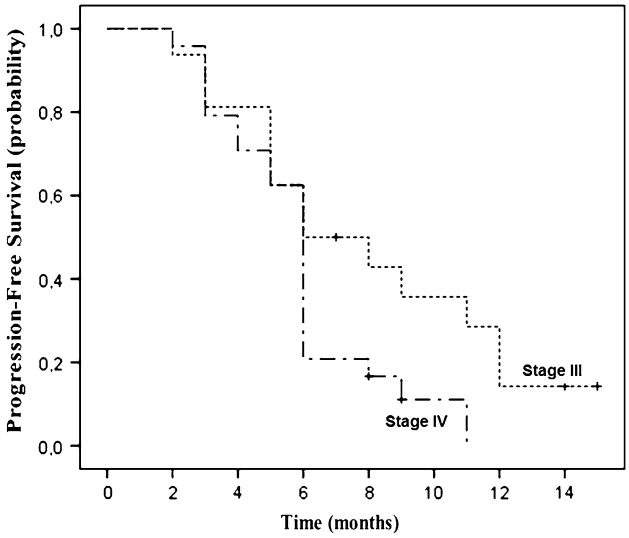

Fig. 3 Kaplan–Meier progression-free survival curve of patients treated with gemcitabine, docetaxel and capecitabine, according to stage of the disease

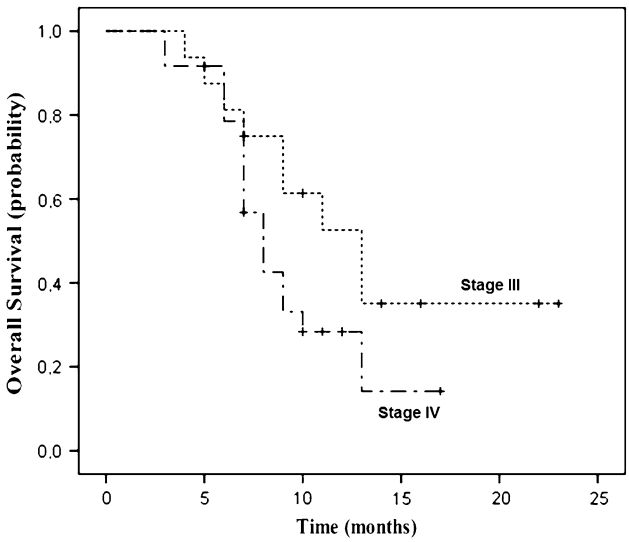

Fig. 4 Kaplan–Meier overall survival curve of patients treated with gemcitabine, docetaxel and capecitabine, according to stage of the disease

unremarkable, easily manageable and not a treatment problem. The incidence of hematologic and non-hematologic toxicities is summarized in Table 3.

Discussion

Although, numerous trials have evaluated a variety of combinations of gemcitabine with traditional cytotoxic or novel targeted agents, until now, gemcitabine has been widely accepted as a standard of care for the first-line treatment of metastatic pancreatic cancer [19], as combination chemotherapy provides only a modest benefit over single agent gemcitabine.

A phase I study of a combination of gemcitabine with docetaxel and capecitabine (GTX regimen) in patients with metastatic pancreatic cancer has been published recently by Hill et al. [10]. The effectiveness of this triple regimen has also been evaluated in two retrospective analyses [11, 12]. Moreover, the results of a prospective phase II study using the GTX regimen in patients with metastatic adenocarcinoma of the pancreas were reported in the 47th ASCO Annual Meeting [13]. In the present study, the GTX regimen

Table 3 Toxicity

Adverse events	Grade			
	1	2	3	4
Neutropenia	4 (10%)	4 (10%)	7 (17.5%)	–
Febrile neutropenia	–	–	–	1 (2.5%)
Thrombocytopenia	4 (10%)	2 (5%)	1 (2.5%)	–
Anemia	7 (17.5%)	2 (5%)	–	–
Nausea/vomiting	8 (20%)	1 (2.5%)	–	–
Anorexia	10 (25%)	2 (5%)	–	–
Diarrhea	6 (15%)	6 (15%)	3 (7.5%)	1 (2.5%)
Constipation	5 (12.5%)	2 (5%)	–	–
Hand-foot syndrome	12 (30%)	7 (17.5%)	3 (7.5%)	–
Fluid retention	7 (17.5%)	3 (7.5%)	–	–
Onycholysis	11 (27.5%)	7 (17.5%)	2 (5%)	–
Alopecia	12 (30%)	26 (65%)	–	–
Conjunctivitis	8 (20%)	–	–	–
Oral mucositis	4 (10%)	2 (5%)	–	–
Asthenia	5 (12.5%)	4 (10%)	–	–
Transaminases elevation	–	1 (2.5%)	–	–
Allergic reactions	–	–	1 (2.5%)	–

was proven particularly effective, as the confirmed tumor regression rate was 40%, with an additional 40% of patients showing stable disease, thus achieving disease control in 80% of patients. Moreover, 62.5% of patients remained without progression for at least 6 months, whereas 38.4% of patients were alive for more than 1 year. These results are in concordance with previously reported response rates with GTX in patients with metastatic pancreatic cancer. Fine et al. [13] in their prospective phase II study reported a response rate of 21.9% along with a 41.5% disease stabilization. The same group in a retrospective analysis of the clinical experience with the GTX regimen reported a response rate of 29% at metastatic sites and stabilization of the disease in 31% of patients [12]. A slightly lower response rate (24.3%) was recently reported in another multicenter review of 70 patients with locally advanced or metastatic pancreatic adenocarcinoma treated with the GTX regimen [11]. Interestingly, in this study, the majority (70%) of patients exhibited stable disease. Similar results (11% partial response; 69% stable disease lasting at least 3 months) were obtained in the phase I study that has been published by Hill et al. [10].

In all four aforementioned studies, the treatment schedule was slightly different to that in our study. Indeed, in both the prospective phase II study and in the retrospective analyses, gemcitabine and docetaxel were administered on days 4 and 11, whereas in the phase I study, docetaxel was given on days 1 and 8 and gemcitabine on days 8 and 15. In all three studies, capecitabine was given for 14 consecutive days in cycles repeated every 21 days. In the present study, gemcitabine and docetaxel were both given on days 1 and 15 and capecitabine on days 1–7 and 15–21 every 28 days. Additionally, in our study, the median delivered dose intensity for each drug was considerably higher to that reported in the aforementioned studies. Although, the efficacy parameters such as response rate, clinical benefit, PFS and 1-year survival in our study are in keeping to that reported in the above trials, the achieved median overall survival of 8 months, in the group of patients with metastatic disease, is considered somewhat inferior. This may partially due to the fact that considerable proportion of patients with stage IV disease (60%) did not receive second-line chemotherapy.

The rationale for developing this triplet regimen was based on earlier reports, which suggest that co-administration of both docetaxel and gemcitabine enhances capecitabine cytotoxic effectiveness. Capecitabine is a prodrug that is converted to its active metabolite 5-FU, by thymidine phosphorylase in the tumor bed, where it inhibits DNA synthesis. As shown in preclinical models, docetaxel modulates and finally increases the activity of thymidine phosphorylase in the conversion of capecitabine to 5-FU. This induction of thymidine phosphorylase activity occurs mainly in tumor tissues and remains for at least 10 days after exposure to docetaxel with maximal activity noted at 4–6 days [20]. Similarly, it has been shown that gemcitabine inhibits ribonucleotide reductase resulting in a depletion of the cellular deoxyuridine monophosphate pools, thereby decreasing competition with 5-FdUMP at the target enzyme thymidylate synthase [21]. There are also preclinical data supporting that sequential exposure to gemcitabine followed by 5-FU increases

significantly the inhibition of thymidylate synthase [22]. Moreover, 5-FU metabolites may inhibit deoxycytidine monophosphate deaminase, an enzyme responsible for the inactivation of gemcitabine [21].

Another triple regimen that demonstrated remarkable activity is the combination of 5-FU with oxaliplatin and irinotecan (FOLFIRINOX). Results from the recently published phase III PRODIGE 4/ACCORD 11 trial evaluating the FOLFIRINOX regimen versus gemcitabine alone in patients with metastatic pancreatic cancer showed dramatic improvements in both median PFS (6.4 months vs. 3.3 months; $P < 0.0001$) and median OS (11.1 months vs. 6.8 months; $P < 0.0001$) in favor of the group receiving FOLFIRINOX [4]. Although, there are some concerns about the toxicity of the FOLFIRINOX regimen (46% of patients' experienced grade 3/4 neutropenia, and in 5.4% of them, this was febrile), 31% of the patients in the FOLFIRINOX group had a definitive degradation of the quality of life versus 66% in the gemcitabine group ($P < 0.001$). The current GTX regimen at the present mode of administration has been proved quite safe and well tolerated. Hematologic toxicity was mild and manageable, as grade 3 neutropenia occurred in 7 (17.5%) patients and febrile neutropenia in one (2.5%). Although, only one-third of patients completed treatment as per protocol, the main reason for treatment discontinuation was disease progression (50%) and only 2 patients (5%) stopped treatment because of treatment-related toxicity (hand-foot syndrome grade 3).

The favorable toxicity profile of the GTX regimen may be due in part to alternative 7 days-on/7 days-off dosing schedule of capecitabine. According to laboratory data reported by Norton et al. [23], capecitabine can potentially be administered safely and effectively at a dose level higher than those recommended. Based on the Norton-Simon mathematical model, investigators found that the time point of maximum impact of treatment averaged from 8.3 to 10.1 days into therapy, with the impact of treatment decreasing thereafter, despite administration for 14 days. Consequently, schedules shorter than 14 days in length can deliver higher dose levels providing optimal benefit associated with a more favorable toxicity profile. In a phase I/II study in patients with advanced colorectal cancer, Scheithauer et al. [24] demonstrated that biweekly administration schedule of capecitabine permits a 30% dose increment compared with conventional capecitabine administration schedules. The same group, in a randomized multicenter phase II trial, showed that dose-intensified biweekly capecitabine plus oxaliplatin seems to be more effective as compared to conventional administration of the two drugs. Moreover, the incidence rate and degree of toxicity between the two schedules were similar [25].

In conclusion, the results of the present study indicate that the combination of gemcitabine with docetaxel and capecitabine is well tolerated and shows a satisfactory degree of activity. The observed efficacy along with that reported from other studies using similar triple combinations suggests that the GTX regimen warrants further evaluation in a phase III clinical trial against the current standard of care.

References

1. Glimelius B, Hoffman K, Sjoden PO et al (1996) Chemotherapy improves survival and quality of life in advanced pancreatic and biliary cancer. Ann Oncol 7:593–600
2. Burris HA III, Moore MJ, Andersen 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 Oncol 15:2403–2413
3. Heinemann V, Boeck S, Hinke A et al (2008) Meta-analysis of randomized trials: evaluation of benefit from gemcitabine-based combination chemotherapy applied in advanced pancreatic cancer. BMC Cancer 8:82
4. Conroy T, Desseigne F, Ychou M et al (2011) Folfirinox versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 364:1817–1825
5. Cunningham D, Chau I, Stocken DD et al (2009) Phase III randomized comparison of gemcitabine versus gemcitabine plus capecitabine in patients with advanced pancreatic cancer. J Clin Oncol 27:5513–5518
6. Herrmann R, Bodoky G, Ruhstaller T et al (2007) Gemcitabine plus capecitabine compared with gemcitabine alone in advanced pancreatic cancer: a randomized, multicenter, phase III trial of the swiss group for clinical cancer research and the central European cooperative oncology group. J Clin Oncol 25:2212–2217
7. Lopes G, Lima CMR (2005) Docetaxel in the management of advanced pancreatic cancer. Semin Oncol 32:10–23
8. Kulke MH, Tempero MA, Niedzwiecki D et al (2009) Randomized phase II study of gemcitabine administered at a fixed dose rate or in combination with cisplatin, docetaxel, or irinotecan in patients with metastatic pancreatic cancer: CALGB 89904. J Clin Oncol 27:5506–5512
9. Blaya M, Lopes Gl, Roman E et al (2007) Phase II trial of capecitabine and docetaxel as second line therapy for locally advanced and metastatic pancreatic cancer. ASCO Annual meeting (Abstract 15029)
10. Hill ME, Li X, Kim S et al (2011) A phase I study of the biomodulation of capecitabine by docetaxel and gemcitabine (Mgtx) in previously untreated patients with metastatic adenocarcinoma of the pancreas. Cancer Chemother Pharmacol 67:511–517
11. De Jesus-Acosta A, Oliver G, Flores E et al (2010) A multicenter review of gemcitabine, docetaxel, and capecitabine (GTX) in patients with advanced pancreatic adenocarcinoma. ASCO Annual meeting (Abstract E14580)
12. Fine RL, Fogelman DR, Schreibman SM et al (2008) The gemcitabine, docetaxel, and capecitabine (GTX) regimen for metastatic pancreatic cancer: a retrospective analysis. Cancer Chemother Pharmacol 61:167–175
13. Fine R, Moorer G, Sherman W et al (2009) Phase II trial of GTX chemotherapy in metastatic pancreatic cancer. ASCO Annual meeting (Abstract 4623)
14. Dakik H, Moskovic D, Carlson P et al (2010) Evaluation of gemcitabine, docetaxel, capecitabine (GTX) in previously treated pancreatic cancer. ASCO Gastrointestinal Cancers Symposium (Abstract 221)

15. Amarantidis K, Houhouli K, Papatheodorou K et al (2006) A dose escalation study of docetaxel plus capecitabine in combination with gemcitabine in patients with advanced solid tumors. Oncol Res 16:281–287
16. Trotti A, Byhardt R, Stetz J et al (2000) Common toxicity criteria: version 2.0. An improved reference for grading the acute effects of cancer treatment: impact on radiotherapy. Int J Radiat Oncol Biol Phys 47:13–47
17. Therasse P, Arbuck SG, Eisenhauer EA et al (2000) New guidelines to evaluate the response to treatment in solid tumors. European organization for research and treatment of cancer, national cancer institute of the United States, national cancer institute of Canada. J Natl Cancer Inst 92:205–216
18. Simon R (1989) Optimal two-stage designs for phase II clinical trials. Control Clin Trials 10:1–10
19. Pancreatic Adenocarcinoma V.2.2010 (2010) In national comprehensive cancer network. Practice guidelines in oncology
20. Sawada N, Ishikawa T, Fukase Y et al (1998) Induction of thymidine phosphorylase activity and enhancement of capecitabine efficacy by taxol/taxotere in human cancer xenografts. Clin Cancer Res 4:1013–1019
21. Heinemann V (2002) Gemcitabine-based combination treatment of pancreatic cancer. Semin Oncol 29:25–35
22. Ren Q, Kao V, Grem JL (1998) Cytotoxicity and DNA fragmentation associated with sequential gemcitabine and 5-fluoro-2′-deoxyuridine in Ht-29 colon cancer cells. Clin Cancer Res 4:2811–2818
23. Norton L, Dugan U, Young Y et al (2005) Optimizing chemotherapeutic dose-schedule (Cds) by norton-simon modeling: capecitabine. In: Presented at the AACR meeting
24. Scheithauer W, Kornek GV, Raderer M et al (2002) Intermittent weekly high-dose capecitabine in combination with oxaliplatin: a phase I/II study in first-line treatment of patients with advanced colorectal cancer. Ann Oncol 13:1583–1589
25. Scheithauer W, Kornek GV, Raderer M et al (2003) Randomized multicenter phase II trial of two different schedules of capecitabine plus oxaliplatin as first-line treatment in advanced colorectal cancer. J Clin Oncol 21:1307–1312