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Fixed dose-rate infusion of gemcitabine in combination with cisplatin and UFT in advanced carcinoma of the pancreas

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Abstract *Background*: Gemcitabine is currently considered the standard treatment for advanced pancreatic cancer (APC). Cisplatin and a fluoropyrimidine have some activity in the treatment of this cancer. The aim of this trial is to evaluate the efficacy and toxicity of a fixed dose-rate infusion of gemcitabine associated with cisplatin and UFT in patients with APC. *Patients and methods*: Forty-six chemotherapy-naïve patients with APC that was either unresectable or metastatic were included in this phase II study. All of them had Karnofsky performance status ≥50 and unidimensionally measurable disease. Treatment consisted of gemcitabine 1,200 mg/m^2 given as a 120-min infusion weekly for three consecutive weeks, cisplatin 50 mg/m^2 on day 1 and oral UFT 400 mg/m^2/day (in two to three daily doses) on days 1 to 21; cycles of treatment were given every 28 days. *Results*: A total of 208 cycles of chemotherapy were given with a median of 4 per patient. Fourteen patients (30%) achieved partial responses (95% CI 19–48%) and 17 (37%) had stable disease. The median time to progression was 5 months, and the median overall survival 9 months. Nineteen patients (49%; 95% CI 32–64%) had a clinical benefit response. Grade 3–4 WHO toxicities were as follows: neutropaenia in 26 patients (57%), with 5 cases of febrile neutropaenia (11%), thrombocytopaenia in 15 (33%), anaemia in six (13%), diarrhoea in 5 (11%), asthenia in 2 (4%) and mucositis in 1 (2%). Seven patients required hospitalisation for treatment-related complications. *Conclusion*: A fixed dose-rate infusion of gemcitabine associated with cisplatin and UFT is active in patients with APC, though at the cost of considerable toxicity.

Keywords Pancreatic carcinoma · Gemcitabine · Cisplatin · UFT · Chemotherapy

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Introduction

Pancreatic exocrine carcinoma is the fifth commonest cause of cancer-related death in Western countries [1]. This disease is characterised by early locoregional spread and distant metastasis. As a consequence, the majority of patients present with advanced disease not amenable to surgical resection. For these patients, systemic therapy has been largely considered ineffective [2, 3], although two small randomised trials showed that chemotherapy improves survival in 4 months with regard to supportive care [4, 5].

Gemcitabine has produced a small but significant advance in this setting. This is a prodrug requiring intracellular phosphorylation by the enzyme deoxycytidine kinase and ultimate conversion to the active difluorodeoxycytidine diphosphate (dFdCDP) and triphosphate (dFdCTP) forms. Gemcitabine 1,000 mg/m^2 given over 30 min every week achieves responses

in 5–15% of patients and ameliorates disease-related symptoms in 24% of them, with a very favourable toxicity profile [6]. As a result, gemcitabine has become the standard chemotherapy for advanced pancreatic cancer (APC). However, median survival, even with gemcitabine treatment, is still under 6 months. Higher doses could improve the results, but pharmacological studies suggest that the mere increment of doses given in 30 min do not increase cytotoxicity or the therapeutic index. This is probably because the enzyme deoxycytidine kinase is saturated at concentrations of 15–20 μM of gemcitabine. Such a concentration is reached with doses ≥350 mg/m^2 given in 30 min. Alternatively, increasing the infusion time while holding the dose rate constant at 10 mg/m^2/min could result in increased intracellular levels of the active metabolites dFdCDP and dFdCTP, thus enhancing the activity of gemcitabine [7]. As a matter of fact, a randomised phase II trial showed that the administration of gemcitabine at a fixed-dose rate increased median survival in 3 months compared to its administration in 30 months (8 vs 5 months) [8].

Single-agent cisplatin demonstrated a tumour response rate of 21%, with a median response duration of 5 months [9]. In vitro and in vivo studies of gemcitabine and cisplatin have demonstrated synergy [10]. Phase II trials with this combination have yielded a response rate of 11–31% and a median survival of 7–8 months. [11, 12]. The results of a phase III trial that compared cisplatin and gemcitabine versus gemcitabine showed that the combination increases both the overall response rate (26 vs 9%) and the median time to disease progression (20 vs 8 weeks), but although median survival was also prolonged (30 vs 20 weeks) no statistical significance was achieved [13].

5-Fluorouracil (5-FU) has been frequently used in the treatment of APC, with a wide range of reported activities for bolus and continuous infusion (0–20%) [1]. Higher response rates (17–43%) have been reported in phase II trials with 5-FU-based combinations [14, 15], but these results have not been confirmed in randomised trials [16]. When 5-FU is given as a continuous infusion, 5-FU mainly acts by inhibiting thymidilate synthase, an enzyme involved in pyridimidine nucleotide synthesis. This mechanism suggests a possible synergism between the fluoropyrimidines and gemcitabine, because the latter inhibits deoxycytidine kinase, a key enzyme in the salvage pathway of pyrimidine synthesis [17]. Phase II trials of infusional 5-FU and either cisplatin or gemcitabine have shown higher response rates and longer median survivals than historical control patients [18–20]. Although therapy with 5-FU could have some advantages, continuous infusion requires the use of infusion pumps that increase the risk of problems associated with central venous lines. For this reason, oral fluoropyrimidines may represent a convenient and more acceptable therapeutic modality.

UFT, an oral fluoropyrimidine that is absorbed in the intestine, is a combination of 1-(2-tetrahydrofuryl) 5-fluorouracil (tegafur) and uracil in a 1:4 molar ratio. Tegafur is hydroxilated and converted to 5-FU by hepatic microsomal enzymes. Uracil inhibits the catabolism of 5-FU, thus increasing its plasma concentration [21]. In a pharmacokinetic study, UFT 370 mg/m^2 given orally on a 28-day schedule resulted in blood concentrations comparable to those following a continuous intravenous infusion of 5-FU 250 mg/m^2 [22]. The experience with this drug in the treatment of APC is limited. A retrospective analysis compiled the Japanese experience in a variety of tumours and reported a 25% response rate. Despite, a recent phase II trial has shown that UFT administered alone had no beneficial effect on survival or clinical response [23]. Other studies showed that the association of gemcitabine and UFT, with or without leucovorin, produced response rates of 16–23% with median survivals of 5.8–7 months [24–26]. In a previous study of our group, using the combination of UFT and gemcitabine administered at a fixed dose-rate, we obtained a response rate of 33% and a median survival of 11 months [27]. These results suggest that UFT has some activity on APC.

In addition, it has been reported that a four-drug combination (gemcitabine, 5-FU in continuous infusion, cisplatin and 4-epirrubicine) yielded an overall response rate of 41%, with a median survival of 10 months [28]. These results lay the foundations for new studies employing combinations of three or more drugs that could hopefully improve current treatment outcomes in APC. For this reason we sought to explore if the addition of cisplatin to the combination of gemcitabine and UFT could improve the results of this association. This regimen would take advantage of the synergism between gemcitabine, cisplatin and fluoropyrimidines. To this end the doses of gemcitabine and UFT were not modified with respect to our previous study [27], and cisplatin was added according to the regimen of Reni et al. at a dose of 50 mg/m^2 [28]. The main objective of the present study was to assess the antitumour activity and toxicity of this regimen in patients with locally advanced or metastatic pancreatic exocrine cancer.

Patients and methods

Patient population

From May 2002 to September 2003, 46 patients with histologically or cytologically confirmed APC entered into this study. Eligible patients had: (1) locally advanced or metastatic disease not potentially curable by other therapeutic modalities; (2) Karnofsky performance status of at least 50%; (3) an estimated life expectancy of at least 3 months; (4) at least 2 weeks recovery from any surgical procedure; (5) adequate bone marrow function, that is, a granulocyte count of 2×10^9/l or greater, and a platelet count over 100×10^9/l; (6) normal renal function, as defined by a serum creatinine level of less than 115 μmol/l and creatinine clearance over 60 ml/min; (7) adequate hepatic function, that is, serum

bilirubin of less than 35 μmol/l, serum glutamic oxalacetic transaminase (SGOT) and serum pyruvic transaminase (SGPT) levels less than three times the upper normal limit, unless these alterations were due to metastatic disease, in which case an increase up to five times the upper normal limit was allowed. Patients with any prior chemotherapy for advanced disease, brain or meningeal metastases, or a history of any other malignancy, were excluded, except in cases of basal cell carcinoma or in situ cervical carcinoma adequately treated. Patients provided written informed consent according to directives of local ethical committees of all participating institutions.

All patients had unidimensionally measurable disease, as defined by Response Evaluation Criteria in Solid Tumors (RECIST) [29]. Pleural effusion, ascites, osteoblastic lesions or previously irradiated lesions were not accepted as measurable disease. Patients who had received radiotherapy were eligible if there was at least one measurable lesion outside the radiation field. Eligible patients for clinical benefit assessment had one or more of the following requirements: base line Karnofsky performance status less than 80, baseline analgesic consumption of at least 10 morphine-equivalent milligrams per day, or baseline pain intensity score of at least 20 mm (maximum 100 on the Memorial Pain Assessment Card) [30].

Treatment plan

The study regimen consisted of gemcitabine 1,200 mg/m^2 in 120 min on days 1, 8 and 15, given through an infusion pump; cisplatin 50 mg/m^2 on day 1 after gemcitabine infusion and hydration, and oral UFT 400 mg/m^2/day (in two to three doses) on days 1–21. Pills were taken before meals to favour absorption. Courses were repeated every 28 days for a minimum of two per patient, unless progressive disease was detected. Responding patients continued therapy until progression or the appearance of unacceptable toxicity. Patients with stable disease and clinical benefit continued therapy whenever symptomatic relief persisted or until the appearance of unacceptable side effects. Patients with stable disease and no clinical benefit received a maximum of six courses.

Toxicity for each course was recorded before the next treatment course and graded according to WHO scales [31]. Therapy was delayed for 1 week if the neutrophil count was $<1.5\times10^9$/l or the platelet count $<100\times10^9$/l on the first day of the course. Therapy was definitely discontinued if toxicity persisted after a 2-week delay. During a course, the gemcitabine dose was reduced to 50% of previously administered if the neutrophil count was between 0.5 and 1×10^9/l or when the platelet count was between 50 and 74×10^9/l. No gemcitabine was given if lower levels were found [8]. If the patient experienced grade 4 neutropaenia or thrombocytopaenia, UFT was withheld until recovery to the grade 3 level. Also, if there were grade 4 haematological toxicities or in case of grade 3 toxicity repeated in two occasions, the dose of gemcitabine was reduced by 25% in subsequent courses. In the case of grade 3–4 diarrhoea, the UFT was interrupted and the dose was reduced by 25% in the following courses. In the case of renal impairment (creatinine clearance <60 ml/min) the dose of cisplatin was reduced by 25% in the following courses. In case of grade 3–4 neurotoxicity, cisplatin was interrupted. For the rest of grade 3–4 non-haematological toxicity, the doses of gemcitabine, cisplatin and UFT were reduced by 25% in subsequent courses.

Pre-treatment and follow-up studies

Patients had a full clinical history, physical examination, performance status assessment, haematological and biochemical profiles (including CA19-9 level), a chest X-ray and a computed tomography scan of the chest and abdomen at baseline. Additional imaging investigations were performed if clinically indicated. While on study, patients were followed weekly to assess toxicity, Karnofsky performance status, analgesic consumption and pain. A blood analysis including haematological counts, serum chemistry and creatinine level was also performed weekly. A computed tomography scan was repeated every two courses to assess objective response. At the end of chemotherapy, all clinical, laboratory and imaging studies were repeated and patients underwent follow-up examination every 2 or 3 months until death.

Toxicity and response criteria

Toxicity for each course was recorded and graded according to WHO scales [31]. For toxicity analysis, the worst toxicity for each patient across all courses was used. Patients were evaluated clinically on an intent-to-treat basis at least every 4 weeks and radiographically every 8 weeks. For each patient, tumour measurements were made by the same investigator throughout the study. For evaluating the lesions, same technique was used throughout the treatment period to ensure consistency of consecutive measurements. In addition, a panel composed of two radiological experts external to the study reviewed source documents of all patients with an objective response or disease stabilisations reported by the investigator. RECIST response guidelines were used [29] defining all responses after at least 8 weeks of therapy as follows: complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD). All responses were confirmed ≥4 weeks later. Time to tumour progression was estimated by the product limit estimation from the date of the first course to the first evidence of disease progression. Survival was calculated by the same method from the date of the first course until the date of death or last known follow-up.

Clinical benefit was evaluated according to previously established criteria [6, 32]. Clinical benefit response depended on pain assessment (pain intensity and analgesic requirements), performance status and weight loss. Patients with a clinical benefit response should have an improvement in one or more of these parameters for at least 4 weeks, without worsening in any of the others.

Statistical analysis

The primary end point was the response rate and the secondary objectives were the clinical benefit, survival and time to progression. Dose intensity was calculated by dividing the total mg/m^2 of drug given by the number of weeks elapsed from the beginning of therapy to the end of the last cycle.

An optimal two-stage design as described by Simon [33] was used. In the first stage, a total of 13 patients were included and at least four responses (both complete and partial responses) were required to continue to the second stage. In the second stage, 30 additional patients were included plus a 10% to allow for losses. Thirteen responses were needed to conclude with a 95% confidence that the response rate was greater than 40%. The Wilcoxon rank sum method was used to compare quantitative variables, the Fisher's exact test for percentages, and the Kaplan–Meier method for survival, time to tumour progression and the duration of response.

Results

Patient population

Forty-six patients were enrolled onto the study. Table 1 outlines their clinical characteristics. Eleven patients had locally advanced disease that was surgically unresectable (24%). The remaining 35 patients (76%) had metastatic disease, including 6 patients with previously resected tumours who developed distant recurrent disease. All subjects were assessable for toxicity and responses. Seven patients were not assessable for clinical benefit because they had a Karnofsky performance status over 70% and no pain at entry.

Table 1 Patients' characteristics

Characteristics	No. of patients
Gender [median age 57 years, range (27–77)]	
Male	30 (65%)
Female	16 (35%)
Karnofsky Performance status	
100–80	28 (61%)
70–50	18 (39%)
Pain score (range)	
0–19	12 (26%)
20–49	18 (39%)
50–100	16 (35%)
Weight loss	
None	6 (13%)
1–10%	23 (50%)
>10%	17 (37%)
Disease at presentation	
Locally advanced	11 (24%)
Metastatic disease	35 (76%)
Sites of metastatic disease	
Liver	26 (74%)
Lymph nodes	7 (20%)
Lung	5 (14%)
Peritoneum	4 (11%)
Others	4 (11%)

Treatment summary

A total of 208 cycles were administered with a median of 4 cycles per patient (range 1–11). Four patients received less than three courses: three had progressive disease, whereas the other decided to withdraw from the study after the first course. All patients were included for response and survival calculations on an intent-to-treat basis.

The median dose intensity was 693 mg/m^2/week for gemcitabine, 11 mg/m^2/week for cisplatin, and 1,806 mg/m^2/week for UFT, which corresponded to 77, 89 and 86% of the planned doses, respectively. Weekly doses of gemcitabine were reduced by 25% in 12 patients (24%) due to previous haematological toxicities; the doses of cisplatin were reduced in 3 patients (6%) due to the elevation of creatinine levels and the doses of UFT in 7 (15%) because of diarrhoea. Gemcitabine on days 8 or 15 was skipped in 23% of the courses, and UFT was withheld for 1 week or more in 16% of the courses. Cycles were deferred in 18 patients (39%) at least in one cycle. Ten patients (22%) did not receive gemcitabine on day 15 due to prolonged cytopaenia or bad general medical condition. Haematological toxicity that developed in 14 patients (30%) and personal decisions of 4 patients (9%) motivated the aforementioned data. Five patients (11%) had UFT interruptions of 7–14 days (3 because of toxic reactions and 2 because of non-compliance) and 1 (2%) for more than 14 days due to non-compliance.

Response and survival

Fourteen (30%) of the 46 patients registered onto the study had a partial response (95% CI 19–48%). Seventeen patients (37%) had stable disease and 15 (33%) had a progression. The median duration of response was 7.1 months. Of the 35 patients with metastatic disease, 10 patients (29%; 95% CI 15–47%) had a partial response. Of the eleven patients with locally advanced disease, the objective partial response rate was 36% (95% CI 11–71%). Eight of the 11 patients without metastasis subsequently received chemoradiotherapy. Response was not related to the location of metastases or the percentage of weight loss. The Karnofsky

performance status did not influence the probability of a response (41% if ≥80 vs 26% if <70; difference non-significant). At the time of analysis, disease had progressed in 39 patients (84%). The median time to progression was 5 months (95% CI 4.7–6.2). After a medium follow-up of 11 months (range 2–17), 35% of the patients were alive. The median overall survival was 9 months (95% CI 7.2–14.4). The 6-month and 1-year actuarial survival rates were 72 and 32%, respectively. Among 44 patients with determined baseline CA19-9 levels, CA19-9 was reduced by 50% or more in 23 patients (52%). The median survival in patients with ≥50% CA19-9 decline during treatment was 10.1 months while it was 5 months in the rest of the group.

Thirty-nine patients had symptoms at entry. Eighteen patients had a low Karnofsky performance status at entry: seven (39%) improved, whereas six (33%) remained stable and five (28%) worsened (Table 2). Thirty-four patients had a baseline pain intensity score of at least 20 mm: 14 (41%) improved without increasing analgesia, 10 (30%) remained stable, and 10 (29%) worsened. Thirty-seven patients consumed more than 10 morphine-equivalent milligrams at entry: 11 (30%) reduced the consumption, 16 remained stable (43%) and 10 (27%) increased the consumption. Seventeen patients had significant weight loss at entry: 5 (29%) experienced a weight gain of at least 10%, 8 (47%) remained stable and 4 (24%) lost weight. As a whole, 21 patients (49%; 95% CI 32–64%) had a clinical benefit response.

Toxicity

All 46 patients were evaluable for toxicity (Table 3). The chemotherapy regimen was generally well tolerated, the main side effects being gastrointestinal and haematological. No toxic deaths were recorded. Seven patients required hospitalisation for treatment-related complications (febrile neutropaenia, $n=5$ and diarrhoea, $n=2$) Grade 3–4 toxicities were as follows: neutropaenia in 26 patients (57%), with 5 (11%) cases of febrile neutropaenia, anaemia in 6 (13%), thrombocytopaenia in 15 (33%), diarrhoea in 5 (11%), asthenia in 2 (4%) and mucositis in 1 (2%).

Discussion

In spite of its modest efficacy, gemcitabine is currently considered the standard treatment of APC. In order to improve patients' outcome a number of schemas that combine gemcitabine with other cytotoxics have been developed. Phase II trials have yielded promising results, with higher response rates (11–45%) and longer median survivals (6–11 months) [20, 27, 34, 35]. However, randomised trials have failed to demonstrate a consistent improvement in survival time [13, 16, 36–41]. In this regard, it is necessary to implement new treatment endeavours.

One strategy has focused on the development of combinations that seek to exploit the aforementioned synergism between gemcitabine, cisplatin and fluoropyrimidines. In the current trial, we tried to make the most of gemcitabine, cisplatin and a fluoropyrimidine. The schedule of administration of UFT tried to simulate the effects of a continuous infusion of 5-FU, whereas gemcitabine was optimised through the use of a fixed dose-rate of 10 mg/m^2/min. In our study, a response rate of 30%, a median survival time of 9 months, and a clinical benefit in 54% of the patients suggest that the combination of gemcitabine–cisplatin–UFT is an active schema in the treatment of APC.

Table 2 Effect of treatment on the Karnofsky performance status and symptoms in 39 patients evaluable for clinical benefit

Variable	No. of patients evaluable	Improvement	No change	Worsening
Performance status	18 (39%)	7 (39%)	6 (33%)	5 (28%)
Pain	34 (74%)	14 (41%)	10 (30%)	10 (29%)
Analgesic consumption	37 (80%)	11 (30%)	16 (43%)	10 (27%)
Weight loss	17 (37%)	5 (29%)	8 (47%)	4 (24%)

Clinical benefit response: 49% (95% CI, 32–64)

Table 3 Worst toxicity per patient (WHO Grades) during the whole trial

Toxicity	Per patient ($N=46$)		Per cycle ($N=208$)	
	Grade 3	Grade 4	Grade 3	Grade 4
Neutropaenia	21 (46%)	5 (11%)	23 (11%)	6 (3%)
Thrombocytopaenia	15 (33%)		19 (9%)	
Anaemia	6 (13%)		12 (6%)	
Nausea/vomiting	6 (13%)		10 (5%)	
Diarrhoea	4 (8%)	1 (2%)	6 (3%)	2 (1%)
Stomatitis	1 (2%)		2 (1%)	
Asthenia	2 (4%)		4 (2%)	

Although these results compare favourably with those obtained with single-agent gemcitabine, they do not seem to improve our own results with the same scheme without cisplatin, which produced a 33% response rate and a median survival time of 11 months. However, a comparison of the efficacy between both regimens should be done with caution, as there is no direct comparison and the clinical characteristics of the patients could be different. In fact, the patients included in the present study could have a more favourable prognosis than those in the former trial (24 vs 19% with locally advanced disease and 61 vs 40% with Karnofsky performance status ≥80) [27]. Therefore, it does not seem that the addition of cisplatin to the combination of gemcitabine and UFT has improved its clinical efficacy.

Our results resemble those reported in two phase II studies that evaluated the efficacy of the association of gemcitabine, cisplatin and continous 5-FU infusion. They showed response rates of 19 and 23%, with median survival times of 9 and 8.6 months, respectively [42, 43]. These results are similar to those achieved with two-drug combinations [20, 27, 34, 35]. For this reason the addition of a third drug does not probably improve patients' outcome. However, given the lack of phase III head-to-head comparative trials caution is advised when making such comparisons, since differences between patients' characteristics can bias the results. On the other hand, a combination of cisplatin, gemcitabine, 5-FU in continous infusion and epirubicin has been studied in 59 patients. Fifty-one percent of them had a response, 78% had a clinical benefit and the median survival was 10 months [28]. A subsequent randomised phase II trial compared this schema with gemcitabine alone, reporting a significant improvement in time to progression at 4 months (60 vs 28%), response rate (40 vs 8.5%), and 1-year survival rate (38 vs 22%). However, no data was mentioned regarding the median survival time [44].

As the goal for APC therapy is mainly palliative, today, toxicity and convenience for patients are important issues in addition to efficacy. Our patients mainly suffered haematological side effects, with 57% grade 3–4 neutropaenia and 33% grade 3 thrombocytopaenia. Also, 15% of patients required admission to hospital as a result of treatment-derived complications. It can be mentioned that the optimal dose of cisplatin in combination with the regimen gemcitabine–UFT had not been previously determined in a phase I trial. However, the employed dose of cisplatin was relatively low, and the first 19 patients were closely monitored and found to be without excessive toxicity. Anyway, this toxicity is similar to that described with the combination of cisplatin, gemcitabine and 5-FU in continous infusion (60% of patients with grade 3–4 neutropaenia) [42] and inferior to that reported with the incorporation of 4-epirubicine (84% of the patients with neutropaenia) [28]. Probably, profilactic usage of colony-stimulating growth factors can diminish the incidence of neutropaenia and prevent the development of febrile neutropaenia events. On the other hand, oral fluoropyrimidines avoid the cost and inconveniences of infusion pumps, thus reducing interference with daily life.

Conclusion

In conclusion, a fixed dose-rate infusion of gemcitabine associated with cisplatin and UFT is active in patients with APC, though at the cost of considerable toxicity. However, other two-drug combinations have shown similar efficacy with less side effects, making them more appealing options for further studies. In addition, promising preliminary results of other agents in combination with gemcitabine, such as bevacizumab, cetuximab or erlotinib, do warrant further evaluation [45–48].

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