Gemcitabine and Continuous Infusion of 5-Fluorouracil in Locally Advanced and Metastatic Pancreatic Cancer: A Phase I-II Study

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Abstract. Background: Gemcitabine has been recently recognized as standard treatment in advanced pancreatic cancer. To potentiate its single-agent activity we conducted a phase I-II study with the primary objective of establishing the maximum tolerable dose (MTD) of gemcitabine and continuous infusion 5-FU in patients with locally advanced or metastatic pancreatic cancer. Patients and Methods Fifteen patients received a fixed dose of 5-FU 200 mg/m² protracted infusion for six months. Gemcitabine was administered weekly for three out of four weeks for six cycles at escalating doses of 800 mg/m² to 1100 mg/m². Results: MTD was established at 1000 mg/m² of gemcitabine. Of the 11 evaluable patients, 7 patients had stable disease, 1 had partial response and 3 had progressive disease. Of the 14 patients evaluable at follow-up, median time to progression was 5 months. Median survival was 10 months. Conclusion: This study confirms the good tolerability of the combination, of gemcitabine with 5-FU.

Chemotherapy has been proposed in the past, but in clinical studies different drugs and regimens have demonstrated no efficacy and discrete toxicity (3). In a multicenter phase II clinical trial conducted by Casper et al. (4), 44 chemonaive patients with advanced pancreatic adenocarcinoma received gemcitabine at doses ranging from 800 to 1500 mg/m² weekly for 3 weeks followed by 1 week of rest. Partial response was seen in 5 patients (11%), with a median response duration of 13 months. Responses were seen in liver metastases as well as in the primary tumours. All responding patients had disease stabilisation or improvement in performance status. Fourteen patients had stable disease for at least 4 months and 9 of these had improvement in performance status. The median survival for the 44 patients treated with gemcitabine was 5.6 months and 23% were alive 1 year after therapy was initiated. Overall, toxicity was mild.

In a phase II European study conducted by Carmicheal et al. (5), chemonaive patients with advanced pancreatic cancer received gemcitabine at doses ranging from 800 to 1000 mg/m² by 30-minute intravenous infusion once weekly for 3 weeks with 1 week of rest. Of the 32 patients enrolled, 23 were evaluable for efficacy and received at least 2 courses of gemcitabine. Two patients (9%) had independently documented partial response accompanied by decreases in CA 19.9 and CEA, plus pain relief and reduced analgesic requirement. Six patients had stable disease for at least 2 courses of gemcitabine. Two patients (9%) had independently documented partial response accompanied by decreases in CA 19.9 and CEA, plus pain relief and reduced analgesic requirement. Six patients had stable disease and overall median progression-free survival was 11.2 + weeks (range 4 to 28 weeks). No WHO grade 4 haematological toxicity occurred except in patients who progressed, although leucopenia and thrombocytopenia were the most common reasons for limiting or omitting dosages.

5-Fluorouracil (5-FU) has been the most widely used agent in gastrointestinal malignancies. A randomised, multicenter study of 126 symptomatic chemonaive patients by Burris et al. (6) compared gemcitabine and 5-FU in the treatment of advanced pancreatic cancer. Patients were randomised to
1000 mg/m² of gemcitabine for 30 minutes once weekly for 7 weeks, followed by 1 week of rest, then once weekly for 3 out of every 4 weeks, or to 600 mg/m² of 5-FU weekly over 30 minutes. The toxicity profile of the two drugs differed, with more frequent gastrointestinal symptoms (diarrhoea, vomiting) in the patients treated with 5-FU and more pronounced haematological side-effects (neutropenia, thrombocytopenia) in the patients who received gemcitabine.

The primary endpoint of the study was clinical benefit response that included pain intensity, performance status and weight gain in 23.8% of the gemcitabine group compared to 4.8% in the 5-FU group; median survival was 5.65 months versus 4.41 months, respectively ($p=0.0025$). This study confirms the clinical and survival benefit of gemcitabine treatment in chemotherapy patients with pancreatic cancer.

Rothenberg et al. (7) investigated gemcitabine in patients with pancreatic cancer who had progressive disease while receiving 5-FU. In this prospective, multicenter phase II trial of patients with locally advanced or metastatic adenocarcinoma of the pancreas, clinical benefit response was designed to be the primary endpoint. Gemcitabine was administered at a dose of 1000 mg/m² by 30-minute intravenous infusion weekly for 7 weeks, followed by a week of rest, then weekly for 3 out of 4 weeks thereafter. The median survival, a secondary endpoint for the study, was 3.85 months. The median time to progressive disease (PD) was 2.53 months. These data show that gemcitabine provides marked and sustained clinical benefit for patients with pancreatic carcinoma who fail 5-FU chemotherapy.

Recent studies in the treatment of colorectal cancer suggest that 5-FU may be a more effective and better tolerated agent when given as a continuous intravenous infusion. Hansen et al. (8) reported a 19% partial response rate in 16 patients with metastatic pancreatic cancer. Hidalgo et al. (9) reported a phase I-II study of gemcitabine in combination with continuous infusion of 5-FU 200 mg/m². A maximum tolerated dose (MTD) of 1000 mg/m² for gemcitabine was demonstrated in this study and the therapy was well tolerated (9).

In view of the single-agent activity and different toxicity profiles of gemcitabine and 5-FU and the encouraging results with the continuous infusion of 5-FU, we conducted a phase I-II study with the primary objective of establishing the maximum tolerated dose (MTD) of gemcitabine and continuous infusion 5-FU in patients with advanced pancreatic cancer. Secondary objectives included the assessment of the toxicity profile, the objective response rate and symptomatic benefit (clinical benefit) of the combination of gemcitabine and fluorouracil.

**Patients and Methods**

*Eligibility criteria.* Patients included in the study, between 18 and 75 years of age, had to have a histological or cytological diagnosis of pancreatic adenocarcinoma, locally advanced or metastatic, not amenable to surgery of curative intent and had to be chemo naïve with a performance status of 60 or higher. They had to have an estimated life expectancy of at least 12 weeks and adequate bone marrow reserve. Lesions serving as measurable disease had to have been at least one cm by one cm as defined by imaging techniques (CT or MRI) or physical examination. Patients had not to have central nervous metastases, serious concomitant systemic disorders, second primary malignancy, ascites or third space fluid.

Informed consent was obtained from all patients.

**Study design.** All patients were enrolled to receive gemcitabine and 5-FU in this single-arm trial. The study consisted of a dose-finding design comprising several levels of dose escalation of gemcitabine to determine the MTD, defined as the highest dose that could be safely administered to a patient producing tolerable, manageable and reversible toxicity. Each dose level was planned to enrol between 3 to 6 patients. If, in the course of escalating dose levels, WHO grade 4 haematological toxicity or grade 4 nausea and vomiting or any other non-haematological WHO grade 3 toxicity, excluding alopecia, occurred in 1 out of 3 patients, this event was considered to be a dose-limiting toxicity (DLT) and 3 additional patients were to be treated at the same dose level. In the event of the same toxicity occurring in 1 of these 3 patients, the MTD was established at that dose level. There was no inpatient dose escalation.

**Treatment plan.** Gemcitabine was supplied as a lyophilized powder in sterile vials. The drug was prepared with normal saline and administered as a continuous infusion over approximately 30 minutes. Fluorouracil was supplied as a lyophilized powder and administered over a continuous infusion through a permanent venous access catheter *via* a multi-day Travenol pump or CADD-1 pump. Gemcitabine was given on days 1, 8 and 15 of each 28-day cycle. A cycle was defined as 3 consecutive weeks of treatment followed by a week of rest. The dose escalation scheme of gemcitabine comprised three levels of 800, 1000 and 1100 mg/m². Fluorouracil was given at the dosage of 200 mg/m²/day as a protracted venous infusion (PVI). Treatment was to continue for no more than 6 cycles. In the event of disease progression, patients were taken off the study and offered second-line treatment at the discretion of the treating physician.

Dexamethasone 8 mg was administered just before gemcitabine infusion. Metoclopramide, 30 mg in 100 ml normal saline on the days of gemcitabine treatment, was given as antiemetic prophylactic therapy. Patients could have received full supportive care including growth factors for prolonged myelosuppression.

No treatment reduction was planned for grade 1 toxicity. Gemcitabine was given at 75% of the total dose if grade 2 haematological or grade 3 non-haematological toxicity was detected and at 50% of the total dose for grade 3 haematological toxicity. 5-FU was reduced to 75% of the total dose for grade 2 diarrhoea and mucositis and for grade 3 haematological toxicity (thrombocytopenia). In the event of grade 3 diarrhoea, mucositis or cutaneous toxicity, both 5-FU and gemcitabine were omitted until recovery. Patients were taken off the study if recovery took longer than 2 weeks. Therapy was discontinued for any grade 4 toxicity.

**Duration of treatment and efficacy measures.** No more than 1 week before enrolling into the study, the disease status of each patient was assessed by medical history and physical examination, evaluation of analgesic use for pain, evaluation of weight and performance status (according to the Karnofsky scale) and tumor measurements of palpable lesions. No more than 2 weeks before
enrolment, each patient was assessed by abdominal CT scan, chest X-ray and biochemical evaluation including CEA and CA 19.9. Tumor response was determined every 2 cycles using the same clinical, radiological and biochemical evaluations used at baseline. A panel of independent experts evaluated the response of each investigator-determined responder to gemcitabine and 5-FU therapy by applying standard WHO criteria. Unidimensionally measurable disease, lesions in previously irradiated fields, ascites, pleural effusions, plastic or mixed bone metastases, and abdominal masses clinically detectable but not measurable, were considered non-evaluable.

The duration of a partial response (PR) was measured from the time of the assessment of the PR until the time of documented progressive disease. The duration of complete response (CR) was measured from the time the CR was documented until the date of the first observation of disease progression. Survival was measured from administration of the first dose until the date of death.

To be considered assessable for clinical benefit response, patients had to have a Karnofsky performance status less than 80%, a pain score of 20 or more on the Memorial Pain Assessment Card visual analogue scale, weight loss of greater than 10% in the previous 6 months and be taking analgesic therapy. A reduction in pain intensity of at least 50%, a reduction in analgesic consumption of at least 50%, or an improvement of performance status (PS) of at least 20 points for more than 4 weeks, without any worsening of the other parameters, was considered as a positive clinical benefit response. If all three parameters were stable, a weight gain of at least 20 points for more than 4 weeks, without any worsening of the other parameters, was considered as a positive clinical benefit response.

This study was conducted according to Good Clinical Practice standards. The study was approved by the local Ethics Committee. A written informed consent was obtained from all the patients before starting the therapy.

**Results**

**Patient characteristics and dose administration.** From July 1997 to November 1999, 15 patients were enrolled in the study. Between October 1997 (date of accrual of the third patient) and October 1998 (date of accrual of the fourth patient), no patients entered the study. The long accrual time was due to the occurrence of the Di Bella phenomenon in Italy that prevented many patients from accepting chemotherapy trials, especially in the phase I and II setting from January 1997 until the end of 1998 (10). Patient characteristics are summarised in Table I. Seven patients had locally advanced and 8 patients had metastatic disease. The median age was 60 years and the PS was more than 80 in 4 patients.

Six patients received 800 mg/m², 6 patients received 1000 mg/m² and 3 patients received 1100 mg/m² of gemcitabine. The total number of cycles completed was 119 of the 143 total planned. Four patients completed the six planned cycles. At the 800-mg/m² level, 53 of the 62 planned cycles were completed, while 49 out of 59 and 17 out of 22 of the planned cycles were completed at the 1000-mg/m² and 1100-mg/m² dose levels, respectively (Table II).

Eight of the 15 patients enrolled were treated with at least one second-line treatment (1 pt oral doxifluoridine; 1 pt cisplatin and 5-FU; 2 pts systemic CPT-11 plus oxaliplatin; 2 pts radiotherapy and 5-FU continuous infusion and 2 pts intraarterial chemotherapy with 5-FU, leucovorin, epirubicin and cisplatin) upon completion or discontinuation of the first-line treatment. Four patients underwent celiac ganglion block, 1 before and 3 after study treatment. The 3 patients who had refused this anesthetic approach before study entry had symptomatic improvement during study treatment; 2 of these patients, however, had this palliative intervention at disease progression.

Of the 360 weeks of 5-FU therapy planned in the study, 239 infusions of 5-FU were omitted or reduced. The reason for discontinuation of the protracted infusion was the induced toxicity. 5-FU-only therapy was modified in 20 of the 47 (42.5%) weeks because of haematological toxicity, mainly thrombocytopenia.

**Toxicity.** The toxicities encountered during the study are summarised in Tables III and IV. At the 800-mg/m² dose level, one patient had a grade 4 haematological toxicity with a severe pancytopenia; a myelocentesis showed only dyserythropoiesis. Combination therapy was stopped and the patient was treated with an oral thymidylate synthesis inhibitor. At the same dose level, a severe allergic reaction occurred in another patient.
after the third infusion of gemcitabine only, since 5-FU had been stopped because of stomatitis. She was taken off the study and successively treated with radiotherapy. In one patient, the occurrence of a renal colic caused the omission of the third gemcitabine dose at the third cycle. Calcium ossalates were present in the urine after the first cycle of therapy (the basal urinalysis was negative). With appropriate hydration, the patient was able to complete the treatment protocol. In another patient, urinalysis revealed calcium ossalates during the study. At the 1000-mg/m² level, a 45-year-old patient had a grade 4 neutropenia and a 73-year-old patient developed oedema in both legs and erysipelas in the right leg during the fourth cycle. Two patients had a grade 4 neutropenia at the 1100-mg/m² dose level. One patient was taken off the study because of a radiological progressive disease after 3 cycles but continued the combination therapy because of the clinical benefit obtained. Out of the study, he continued with 5-FU protracted infusion and gemcitabine administered at a reduced dose of 700 mg/m² every 10 days because of thrombocytopenia for a total of 12 months, maintaining the clinical benefit. Another patient wanted to continue the combination therapy after completing the six cycles planned in the study but he had to discontinue therapy after the seventh cycle because of severe asthenia without progressive disease.

**Activity.** Four patients were taken out of the study before the time of the first re-valuation, 2 because of clinical progressive disease and 2 because of toxicity. Of the 11 patients assessable for response, 7 patients had stable disease upon completion or discontinuation of the study, 1 had partial response and 3 had progressive disease. One patient was lost to follow-up. Of the 14 patients evaluable at follow-up, the median time to progression was 5 months (range 1-10 months). According to an intention-to-treat analysis, the median survival was 10 months (1-38+ months). One patient is still alive at the time of writing (after four cycles of therapy).

**Clinical benefit.** Of the 12 symptomatic patients, 4 had a performance status greater than 80; therefore only 8 patients were evaluable for clinical benefit response. Seven of these patients experienced an improvement of pain intensity expressed in terms of reduction of analgesic consumption and or improvement of performance status.

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<th>Gemcitabine Neutropenia</th>
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**Discussion**

The medical treatment of patients with advanced pancreatic cancer has been problematic for many years, as chemotherapy has seldom been considered a therapeutic option (11). Only recently, a more systematic application of analgesic treatment and an increased recognition of nutrition-related problems have underscored the importance of the management of these patients (12). With the approval of gemcitabine a few years ago on the basis of its symptomatic efficacy and good tolerability in advanced pancreatic cancer patients (4,5), it has become standard therapy in the palliative treatment of this disease, even though data on its efficacy in prolonging survival are scarce (6).

A number of clinical studies have attempted to investigate new combinations of drugs in order to potentiate the efficacy of gemcitabine. First, cisplatin was combined with gemcitabine on the basis of preclinical data (13, 14) showing a synergistic effect between the two drugs; in these studies, the overall response rate ranged from 11% to 31% and overall survival from 7.1 to 8.2 months. Fluorouracil via continuous infusion...
reaction that led to withdrawal of one patient. The MTD was thrombocytopenia. Gemcitabine was the cause of an allergic discontinued in the fourth week of administration because of longer than 6 months. In 20% of the patients, 5-FU was any unexpected toxicities except for progressive asthenia that, in whole, the association of these two drugs did not reveal and diarrhoea and no hand-foot syndrome was observed. On the other, the association of these two drugs did not reveal any unexpected toxicities except for progressive asthenia that, in responding patients, did not allow therapy to continue for longer than 6 months. In 20% of the patients, 5-FU was discontinued in the fourth week of administration because of thrombocytopenia. Gemcitabine was the cause of an allergic reaction that led to withdrawal of one patient. The MTD was established at 1000 mg/m² gemcitabine, with the DLT being haematological toxicity. The relative response rate was inferior to that reported in the Spanish study (3.7% vs. 19.2%) with no complete responses; however, the discrepancies in the evaluation of responses may reflect the difficulties in establishing dimensional parameters with classical imaging techniques in this neoplasia. The role of new evaluation methods, like positron emission tomography (PET), has to be established in future studies. The difference in time to progression (5 vs. 7.4 months) is possibly related to the more frequent clinical and subsequently radiological evaluation in our study. The overall survival time compares quite well between the two studies (10 vs. 10.3 months) (9). The cytological diagnosis of the long survivor in our study was revised and confirmed. We could not evaluate the clinical benefit response in a high percentage of patients due to their good performance or lack of symptoms at study. Therefore our study failed in fulfilling its secondary aim. Recently clinical benefit, as evaluated in the clinical trial setting up to now, has been under discussion as a significant end point in this type of neoplasia for future trials (16).

In the last 3 years, gemcitabine has been combined with 5-FU in different schedules. When combined with bolus 5-FU (17), gemcitabine obtained a median overall survival lower than that obtained with protracted 5-FU infusion alone. The potentiation of bolus 5-FU with leucovorin in combination with gemcitabine (18) led to diarrhoea in a number of cases. This toxicity, although of moderate grade, is highly undesirable in these patients. In a French phase II trial, gemcitabine was combined with 5-FU and leucovorin using a De Gramont-like schedule (FOLFUGEM) (19). Time-to-event parameters were similar to the 5-FU continuous infusion combinations but the regimen showed heavier myelotoxicity. Furthermore, alopecia occurred unexpectedly in almost all patients. Recently, a phase III study of gemcitabine combined with 5-FU as a weekly bolus vs. gemcitabine alone in patients with advanced pancreatic cancer failed to demonstrate an advantage in median survival for the combination therapy (20). The authors concluded that further studies applying this combination are not compelling despite the bolus administration of 5-FU.

Recently, the combination of gemcitabine and the new oral thymidylate inhibitors has been proposed (21,22). Even though these studies avoid the cumbersome and expensive continuous infusion, the response rate, time to disease progression and overall survival seem not to reach those obtained with the protracted venous infusion combinations.

Other new drugs, which have recently demonstrated a certain activity in monochemotherapy in this neoplasia, have also been combined with gemcitabine in advanced pancreatic patients with low response rates and median survivals that hardly reach 6 months (23-25). Those that show promise in terms of response rate and median survival are combinations with oxaliplatin (with gemcitabine administered at a fixed rate of 10 mg/m²/min) (26) and a four-drug combination regimen named PEF-G (platinum and epirubicin 40 mg/m² on day 1, gemcitabine 600 mg/m² on days 1 and 8 and 5-FU as continuous infusions 200 mg/m²/day on days 1 to 28 of 4-week cycles) (27). Phase III trials applying these two regimens are ongoing. An analysis of the data of the more recent trials shows that both response rate and median survival differ among stage III and stage IV patients. Furthermore, unique strategies have been proposed for advanced locoregional disease (28,29). These findings point to the opportunity to tailor new studies to different subsets of patients.

A number of patients in our study underwent second-line therapy. There is limited experience in the treatment of advanced pancreatic cancer patients who failed in a first-line gemcitabine-containing regimen (30-32). Gemcitabine has also proven useful as salvage therapy in pancreatic cancer to relieve disease-related symptoms and even increase survival (33).

In consideration of the growing assessment of the efficacy and tolerability of gemcitabine in clinical practice (33) and the emerging role of second-line therapy, gemcitabine remains the drug of choice in stage IV patients treated outside clinical trials. Caution should be taken, however, before planning phase III studies in this disease until new phase II studies have adequately evaluated more promising regimens.

References


