Phase II Trial of Gemcitabine and UFT Modulated by Leucovorin in Patients with Advanced Pancreatic Carcinoma

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BACKGROUND. Use of chemotherapy for advanced pancreatic carcinoma (APC) pursues a palliative objective. Gemcitabine is active against this tumor and shows in vitro synergism with 5-fluorouracil. UFT is a combination of tegafur (a prodrug of 5-flouorouracil) and uracil that can be given orally. The administration of UFT for several weeks may simulate the effects of a continuous infusion of 5-fluorouracil. The objective of the current study was to assess the efficacy and toxicity of the combination gemcitabine-UFT-leucovorin in the treatment of APC.

METHODS. Forty-two patients with bidimensionally measurable APC were included. The study regimen consisted of gemcitabine 1000 mg/m^2 once weekly for 3 consecutive weeks, followed by a 1-week rest, intravenous 6S-steroisomer of leucovorin (6SLV) 250 mg/m^2 in 2 hours on Day 1, oral 6SLV 7.5 mg/12 hours on Days 2–14, and oral UFT 390 mg/m^2/day (in 2 doses) on Days 1–14. Cycles were repeated every 4 weeks for a minimum of 3 per patient unless progressive disease was detected.

RESULTS. One hundred eighty-three courses were given, with a median of 4 per patient. World Health Organization Grade 3–4 toxicity was: diarrhea in 7 patients (17%), leucopenia in 2 (5%), nausea/vomiting in 2 (5%), and anemia in 1 (4%). Among 38 patients evaluable for response, 6 achieved a partial response (16%; 95% confidence interval (CI), 6–31.4), 15 had stable disease (39%), and 17 had progression (45%). Improvement in performance status and symptoms (pain, analgesic consumption, and weight) was present in 11 (29%) and 17 (45%) patients, respectively. Eighteen patients (47%; 95% CI, 31.5–54.5) experienced a clinical benefit response.

CONCLUSIONS. The combination of gemcitabine-UFT-6SLV is convenient and moderately active and shows a low toxicity for the palliative treatment of patients with APC. ***Cancer* 2000;89:1706–13.** © *2000 American Cancer Society.*

KEYWORDS: pancreas, pancreatic carcinoma, gemcitabine, UFT, leucovorin, chemotherapy, clinical benefit.

Pancreatic carcinoma represents the fifth leading cause of death due to cancer in Western countries.[1] Greater than 75% of patients present with unresectable tumors, due to either the presence of metastases or invasion in adjacent tissues. The remaining patients have an apparently localized disease, but most of them experience a recurrence after surgery, so 5-year survival remains less than 25%.[2] This means that greater than 90% of patients with pancreatic carcinoma may be candidates for chemotherapy, either at diagnosis or after recurrence.

Chemotherapy has limited activity in patients with pancreatic

carcinoma. Only a few drugs have demonstrated some activity in this disease, 5-fluorouracil (5-FU), cisplatin, adriamycin, mitomycin, and nitrosoureas, all achieving a 10–20% response rate and a median survival of 6 months.[3,4] Despite these poor results, chemotherapy may prolong survival for approximately 4 months compared with supportive care alone, according to the results of 2 randomized trials.[5,6]

5-Fluorouracil remains the mainstay of the treatment for most digestive tumors and has been used extensively for patients with pancreatic carcinoma, either alone or in combination. Its antineoplastic activity depends on the method of administration: as a bolus, the half-life is nearly 15 minutes, which suggests that administration as a continuous infusion might improve efficacy.[7] The activity of 5-FU in continuous infusion is difficult to estimate, because most trials include several drugs. However, a 19% response rate has been reported in a small series.[8] The biochemical modulation of 5-FU by leucovorin increases the response rate in patients with colon carcinoma, but the advantage of such modulation in pancreatic carcinoma is controversial. Two Phase II trials of 5-FU–leucovorin did not find any response,[9,10] whereas the response ranged between 7% and 13% in 2 other trials.[11,12] The response rate was 14% in a trial with 5-FU–leucovorin–interferon.[13]

Gemcitabine may offer some hope in this setting. In a Phase II trial, 11% of patients had a response, and the actuarial 1-year survival was 23%.[14] Gemcitabine then was compared with 5-FU in a Phase III trial: although the response rate to gemcitabine was only 5%, this drug produced significantly better clinical benefit (decreased pain and improved performance status and weight) and survival (5.6 vs. 4.4 months).[15] The addition of 5-FU to gemcitabine might improve the results, and one study demonstrated high in vitro activity of this combination in pancreatic carcinoma cells.[16] Some other drugs such as docetaxel, paclitaxel, irinotecan, and topotecan achieve a response in approximately 10% of patients.[17–19] In view of these considerations, new therapies that improve results and maintain quality of life obviously are needed.

UFT is an oral fluoropyrimidine containing tegafur (1-[tetrahydrofuryl]-5-fluorouracil) and uracil in a molar ratio of 1:4. After activation of tegafur to 5-FU by thymidine phosphorylase, uracil inhibits the catabolism of 5-FU by competitive inhibition of hepatic dihydropyrimidine dehydrogenase, which leads to increased 5-FU levels. This inhibition predominates in tumor cells over normal tissues, so the combination increases the tumor concentration and antineoplastic activity of 5-FU.[21,22] In addition, 5-FU remains in the cell for a longer period when given as UFT.[21,23] In a pharmacokinetic study, UFT at a dose of 370 mg/m^2 on a 28-day schedule resulted in blood concentrations comparable to those after the continuous intravenous infusion of 250 mg/m^2 of 5-FU.[24] These characteristics, along with the possibility of oral administration, make of UFT a noteworthy option for the treatment of digestive neoplasms.

Several years ago, our cooperative group designed a scheme to modulate UFT with leucovorin (LV)[25] Briefly, it consisted of a high dose of intravenous LV—500 mg/m^2 in 2 hours—followed by oral UFT and oral LV for 14 days. The intravenous dose of LV was based on in vitro observations suggesting that the optimal stabilization of the ternary complex and potentiation of 5-FU cytotoxicity is achieved at a total LV concentration of 20 μmol/L in tumor tissue:[26] such a concentration is achievable with high doses of LV, for instance, 500 mg/m^2 in 2 hours.[27] The oral administration of LV after the intravenous dose maintains the cellular deposits of reduced folates during UFT therapy and therefore obtains a continuous modulation. In a Phase I trial, we determined the maximal dose of UFT when modulated by LV.[25] The efficacy and low toxicity of this scheme was demonstrated in a Phase II trial of patients with advanced colorectal carcinoma.[28] The main side effects were gastrointestinal, with 10% of patients presenting Grade 3–4 toxicity, whereas myelosuppression was very uncommon. For this reason, the scheme may be suitable for combination with myelosuppressive drugs: we have reported good results in patients with advanced gastric carcinoma by combining it with etoposide.[29]

Gemcitabine has a toxic profile that differs from that of UFT modulated by LV, so we decided to combine them. Theoretically, this scheme takes advantage of the synergism between gemcitabine and 5-FU, the modulation of tegafur by 6S-steroisomer of leucovorin (6SLV), and the simulation of a continuous infusion of 5-FU. The objective of our Phase II trial was to assess the feasibility and efficacy of this scheme in patients with advanced pancreatic carcinoma (APC).

PATIENTS AND METHODS

From June 1998 to March 1999, 42 patients with histologically or cytologically confirmed APC were entered into the study. Eligible patients had 1) advanced disease not potentially curable by other therapeutic modalities; 2) a Karnofsky performance status of 50 or higher and an estimated life expectancy of at least 12 weeks; 3) a minimum of 2 weeks recovery from any surgical procedure; 4) adequate bone marrow function, that is, a granulocyte count of 2×10^9/L or

TABLE 1
Treatment Scheme

	Dose
Day 1	6S-leucovorin 250 mg/m^2 i.v. UFT 195 mg/m^2 p.o. every 12 hrs
Days 1, 7, and 14	Gemcitabine 1000 mg/m^2 i.v.
Days 2–14	6S-leucovorin 7.5 mg/12 hrs p.o. UFT 195 mg/m^2 p.o. every 12 hrs
Cycles[a]	Every 28 days

UFT: uracil and tegafur combined; i.v.: intravenously; p.o.: orally.
[a] Each patient received a minimum of three cycles, unless progressive disease was detected.

greater and a platelet count greater than 100×10^9/L; 5) normal renal function, as defined by a serum creatinine level less than 1.5 mg/dL and creatinine clearance greater than 60 mL/minute; 6) adequate hepatic function, that is, serum bilirubin less than 35 μmol/L, serum glutamic oxalacetic transaminase and serum pyruvic transaminase levels less than 3 times the upper normal limit, unless these alterations were due to metastatic disease, in which case an elevation up to 5 times the upper normal limit was allowed.

Patients with any prior chemotherapy for advanced disease, brain or meningeal metastases, or history of any other malignancy were excluded, except in the cases of basal cell carcinoma or in situ cervical carcinoma adequately treated. All patients gave informed consent according to the directives of local ethical committees.

All patients had measurable disease that was defined as the presence of at least one lesion measurable by computed scan. Pleural effusion, ascites, osteoblastic lesions, or previously irradiated lesions were not accepted as measurable disease. Patients who had undergone radiotherapy were eligible if there was at least one measurable lesion outside the radiation field.

The study regimen consisted of gemcitabine 1000 mg/m^2 once weekly for 3 consecutive weeks followed by a 1-week rest period, 6SLV 250 mg/m^2 in a 2-hour intravenous infusion on Day 1, oral UFT 390 mg/m^2/day in 2 doses on Days 1–14, and oral 6SLV 7.5 mg/12 hours on Days 2–14. The pills were taken before meals to favor absorption. Courses were repeated every 28 days for a minimum of 3 per patient, unless progressive disease was detected (Table 1). Responding patients continued on therapy until progression or the appearance of serious toxicity. For patients who had clinical benefit only, therapy was continued while this benefit persisted and toxicity was acceptable. Patients with stable disease and no clinical benefit received up to six cycles.

Toxicity for each course was recorded before the next treatment course and graded according to World Health Organization (WHO) scales.[30] Occasionally, patients had gastric pain related to the ingestion of UFT, which is not included in WHO scales. Therefore, we considered it to be of Grade 1–2 if the symptoms improved with antiacids or H2 blockers and Grade 3–4 if the symptoms were intense enough to require the withdrawal of UFT despite the administration of those drugs.[28] Patients were instructed to withdraw from therapy and seek medical advice if they passed three or more liquid stools in a day. In these cases, the dose of UFT was reduced by 25% in subsequent courses. Complete blood counts were obtained before each administration of chemotherapy. If the neutrophil count was between 0.5 and 1.5×10^9/L or the platelet count was between 50 and 100×10^9/L, treatment was delayed for 1 week. After that time, if the neutrophil and platelet levels were recovered beyond those values, the dose of gemcitabine was reduced by 25% in the next cycles. If the neutrophil count was less than 0.5×10^9/L or the platelets count was less than 50×10^9/L, the doses of both gemcitabine and UFT were reduced by 25% after recovery. Therapy was discontinued if toxicity persisted after a 2-week delay. In instances of Grade 3–4 nonhematologic toxicities, the dose of UFT and gemcitabine was reduced by 25% in subsequent courses.

The primary objectives of this Phase II trial were the response rate and the clinical benefit. Secondary objectives were toxicity, survival, and time to progression. Response was evaluated at the end of every three courses following WHO guidelines.[30] Reevaluation was undertaken sooner if there was clinical evidence of progression. Complete response required the total disappearance of all tumors initially observed (determined by two observations not less than 4 weeks apart), with no evidence of new areas of malignant disease. Partial response was defined as a reduction of at least 50% in the sum of the products of the longest perpendicular dimension of all clearly measurable tumor masses (2 observations not less than 4 weeks apart), with no increase in the size of any lesion and no new areas of malignant disease. Stable disease was defined as a decrease in total tumor size less than 50% or a less than 25% increase in the size of 1 or more measurable lesions. There was a progression in the case of a 25% increase in the size of any measurable lesion, the appearance of new areas of malignant disease, or symptomatic deterioration of the performance status by greater than 20%. Death due to disease progression or toxicity occurring before the final evaluation was considered as a therapeutic failure.

Time to tumor progression was estimated by the product limit estimation method from the date of first treatment to first evidence of progression. Response duration and survival were calculated from the first day of therapy until the day of death or last known follow-up.

The criteria to assess clinical benefit have been defined previously.[15,31] Patients evaluable for clinical benefit response initially had 1 of the following signs or symptoms: a Karnofsky performance status less than 80%, a pain score of 20 or more on the Memorial Pain Assessment (MPA) Card visual analog scale (which is considered as clinically significant),[15] consumption of greater than 10 morphine equivalent milligrams of analgesia, and weight loss of greater than 10% in the previous 6 months. A clinical benefit response depended on the assessment of the performance status, pain (pain intensity and analgesic consumption), and weight loss, with a positive result being the sustained improvement (at least 4 weeks) in 1 or more of them without worsening of the others. This evaluation followed the next criteria: positive/negative change in the Karnofsky performance status: improvement/worsening of at least 20 points (stabilization otherwise); positive change in pain: a decrease of at least 50% in morphine-equivalent milligrams or an improvement of at least 50% from baseline in MPA scale; negative change: any increase in morphine consumption or worsening in MPA scale (stabilization otherwise); and positive change in weight: an improvement of 7% or more, excluding third space fluid (negative otherwise).

Dose intensity was calculated by dividing the total amount of the drug given in the first two courses (mg/m^2) by the number of weeks passed from the first dosing to the beginning of the third course. The sample size was calculated to reject a clinical benefit response rate less than 20%. According to the Fleming method,[32] 19 patients were included first. Because the observed response rate was greater 21% in these first 19 patients, the sample was increased to 35 plus 10% to allow for losses, which gives a total of 38 patients evaluable for clinical benefit. Four other patients were included that were evaluable for tumor response but not for clinical benefit response. The Wilcoxon rank-sum statistics were used to compare quantitative variables, and the Fisher exact test was used for percentages. Survival and the duration of response were calculated with the Kaplan–Meier method.

RESULTS

Forty-two patients, 27 men and 15 women, were included in the study. Table 2 outlines their characteristics. Nine patients (21%) had unresectable disease because extensive local infiltration was found at laparotomy. The remaining 33 patients had distant metastases. The median age was 60 years (range, 45–75 years), and the Karnofsky performance status was greater than 70 in 13 patients (31%).

TABLE 2
Patient Characteristics

Characteristic	No. of patients (%)
Gender	
Male	27 (64)
Female	15 (36)
Median age, yrs (range)	60 (45–75)
Karnofsky performance status	
100–80	13 (31)
70–50	29 (69)
Pain score (range)	
0–19	5 (12)
20–49	25 (59)
50–100	12 (29)
Weight loss	
None	3 (7)
1–10%	21 (50)
> 10%	18 (43)
Disease at presentation	
Locally advanced	9 (21)
Metastatic disease	33 (79)
Sites of metastatic disease (n)	
Liver only	14 (43)
Liver plus other	12 (36)
Lung	3 (9)
Lymph nodes	2 (6)
Others	2 (6)

A total of 183 courses of chemotherapy were delivered, with a median of 4 per patient. One patient received 10 courses, and 7 patients received 7 or more courses. Eight patients received less than three courses: five had progressive disease, two died due to unrelated causes (gastrointestinal hemorrhage and cerebrovascular disease), and one moved to another city, where therapy was changed. Another patient died after the third course because of arterial ischemia and before reevaluation. These last four patients were excluded from response assessment. Thirty-eight patients (90%) had symptoms at entry and were assessable for clinical benefit response.

The dose intensity was calculated by adding the dose received in the first 8 weeks of therapy and dividing the result by 8. In the case of UFT, the median dose intensity was 1310 mg/m^2/week, which corresponds to 96% of the projected dose. In the case of gemcitabine, the given dose of 709 mg/m^2/week corresponds to 95% of the planned dose. Three patients received reduced doses of gemcitabine and another

TABLE 3
Therapeutic Results in 38 Patients[a]

Result	No. of patients (%)
Partial response	6 (16)
Stable disease	15 (39)
Progression	17 (45)

[a] Three early deaths, 1 lost for follow-up.

TABLE 4
Effect of Treatment in Karnofsky Performance Status and Symptoms[a]

Variable	Improvement (%)	No change (%)	Worsening (%)
Performance status	11 (29)	17 (45)	10 (26)
Pain	17 (45)	10 (26)	11 (29)
Analgesic consumption	10 (26)	19 (50)	9 (24)
Weight loss	14 (37)	14 (37)	10 (26)

[a] Clinical benefit response: 47% (95% confidence interval, 31.5–64.5).

TABLE 5
Maximum Toxicity per Patient During the Whole Trial

	WHO Grade 1–2		WHO Grade 3–4	
Toxicity	Per patient (%)	Per cycle (%)	Per patient (%)	Per cycle (%)
Nausea/vomiting	13 (30)	15 (8)	2 (5)	2 (1)
Diarrhea	2 (5)	4 (2)	7 (17)	7 (4)
Stomatitis	4 (10)	4 (2)		
Gastric pain[a]	5 (12)	5 (3)		
Neutropenia	4 (10)	6 (3)	2 (5)	2 (1)
Anemia	4 (10)	4 (2)	1 (2)	2 (1)
Thrombocytopenia	4 (10)	4 (2)		
Transaminases	8 (19)	15 (8)		
Asthenia	15 (36)	37 (20)		
Excessive lacrimation	2 (5)	6 (3)		
Alopecia	7 (17)	2 (11)		
Cutaneous rash	4 (10)	6 (3)		
Flu-like syndrome	4 (10)	4 (2)		

WHO: World Health Organization.
[a] Grade 1–2 if it ablated with antiacids or H2 blockers, Grade 3–4 if it was intense enough to require withdrawal of UFT despite therapy with antiacids or H2 blockers.[28]

three reduced doses of UFT (25% reduction in all cases).

Table 3 shows the response. Among 38 patients evaluable for response, 6 had a partial response (16%; 95% confidence interval [CI], 6.1–31.4), 15 had stable disease (39%), and 17 had progressive disease (45%). The median overall survival was 7 months (not reached for responders after a median follow-up of 10 months, 6 months for nonresponders). The 1-year actuarial survival rate was 21%. Response rate was not related to the location of metastases or to the percentage of weight loss, but we found an association between response and performance status: 5 of 12 responses if the Karnofsky was greater than 70 versus 1 of 26 otherwise (42% vs. 4%, $P < 0.01$). The median time to progression was 4 months.

Thirty-eight patients had symptoms at entry. Considering the performance status, 11 patients improved (29%), 17 remained stable (45%), and 10 worsened (26%). Pain improved with no need to increase analgesia in 17 patients, remained stable in 10, and worsened in 11. Fourteen patients (37%) had weight gain. As a whole, 18 patients had a clinical benefit response (47%; 95% CI, 31.5–64.5).

Chemotherapy was well tolerated, the main toxicities being gastrointestinal and hematologic. There were no toxic deaths, and only 3 patients (7%) developed Grade 4 side effects (2 neutropenia and 1 diarrhea). Table 5 displays the worst toxicity per patient. Grade 3–4 toxicities were diarrhea in 17% of patients, nausea/vomiting in 5%, neutropenia in 5%, and anemia in 2%. All the episodes of severe diarrhea occurred in the first course and did not recur after reducing the dose of UFT to 300 mg/m^2. Grade 1–2 toxicities were nausea/vomiting in 30% of patients, asthenia in 36%, transitory rise in transaminases in 19%, gastric pain in 12%, and cutaneous rash in 10%. Four patients experienced a mild flu-like syndrome consisting of myalgias, arthralgias. and fever.

DISCUSSION

The utility of chemotherapy for the treatment of APC has remained controversial until recently and was even formally discouraged.[33,34] This point of view has changed after several randomized studies demonstrated that chemotherapy prolongs survival when compared with supportive care alone[5,6] and produces a clinical benefit by ameliorating some symptoms. Such a benefit does not depend necessarily on objective responses.[15] These results have attracted interest in the development of new regimens.

One way to improve the efficacy of gemcitabine would consist of the administration of higher doses in prolonged infusions. Gemcitabine is transformed into active metabolites (difluorodeoxycytidine diphosphate and triphosphate) through intracellular phosphorylation. The rate of phosphorylation becomes saturated at doses of gemcitabine greater than 10 mg/m^2/minute, so that higher doses do not increase the levels of active metabolites.[35] This has lead to the use of this drug in prolonged infusions. A 17% response

rate was found in a trial of gemcitabine 1500 mg/m^2 given in 150 minutes.[36] Another way to enhance efficacy would be to exploit the synergism between gemcitabine and other cytotoxic drugs, such as cisplatin or the fluoropyrimidines. One in vitro study showed significant synergism between gemcitabine and cisplatin.[37] The results of a trial comparing gemcitabine versus gemcitabine-cisplatin have been reported recently: 10% response versus 31% and 38% clinical benefit versus 45%, respectively.[38] Two other Phase II trials combining gemcitabine and cisplatin have reported responses in 12% and 36% of patients, respectively,[39,40] which suggests improved response for combination chemotherapy over single-agent chemotherapy with gemcitabine.

Some evidence supports the combination of gemcitabine with fluoropyrimidines. Gemcitabine is active in patients with 5-FU refractory APC, which indicates a lack of cross-resistance.[31] Conversely, the main mechanism of action of 5-FU when used in continuous infusion or modulated with leucovorin is the inhibition of thymidylate synthase. This enzyme plays a role in the synthesis of pyrimidine nucleotides. Gemcitabine inhibits deoxycitidine kinase, a key enzyme in the salvage pathway of pyrimidine synthesis,[41] so both drugs ultimately interfere with the same metabolic pathway. In vitro studies in pancreatic carcinoma cells have demonstrated this potential synergism.[16] Recent studies have used 5-FU–gemcitabine for the treatment of APC. One trial combined bolus 5-FU with gemcitabine in 54 patients and reported a 4% response rate and a 51% clinical benefit rate, with a median survival of 7 months.[42] A Phase I–II trial of 5-FU in continuous infusion and gemcitabine included 26 patients: 19% of them responded and 45% obtained a clinical benefit, with a median survival of 10 months.[43] Another study including 48 patients reported responses in 19% of them, clinical benefit in 50%, and a median survival of 8 months with high dose 5-FU in a 48-hour infusion plus gemcitabine.[44] The results of these 2 last trials using 5-FU in continuous infusion are comparable to our results (16% response rate, 47% clinical benefit, 7 months median survival). However, our patients had a more unfavorable clinical profile: metastatic disease in 79% as compared with 65% and 62% in the other trials,[43,44] Karnofsky performance status of 50–70 in 69% as compared with 15% (Eastern Cooperative Oncology Group scale, 2)[43] and 37.5%.[44] Although the routes of administration and the patient characteristics differed in these studies, the results suggest that the continuous administration of fluoropyrimidines in addition to gemcitabine may improve the results of gemcitabine alone.[14,15] A randomized trial is needed to confirm this.

There are only a few studies of UFT in APC. A retrospective study compiled the Japanese experience in a variety of tumors and reported a 25% response rate.[45] An ongoing Phase II trial will determine the activity of UFT-leucovorin in patients with hepatobiliary and pancreatic carcinoma.[46]

Our scheme with an oral fluoropyrimidine avoids the cost and inconveniences of infusion pumps or catheters. In one study of 5-FU in continuous infusion plus epirubicin and cisplatin, 40% of patients with APC experienced complications with their Hickman lines, including thrombotic episodes and the Hickman line falling out.[47] Conversely, our scheme produced low toxicity, mainly gastrointestinal.

In summary, the combination of gemcitabine-UFT-6SLV is moderately active, convenient, and not very toxic in patients with APC, which makes this an appropriate palliative therapy in this setting. The administration of a continuous infusion of gemcitabine or the addition of cisplatin might further enhance efficacy.

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