Phase II study of a fixed dose-rate infusion of gemcitabine associated with uracil/tegafur in advanced carcinoma of the pancreas

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Received 11 March 2002; revised 26 April 2002; accepted 16 May 2002

Background: The objectives of this study were to evaluate the efficacy and toxicity of a fixed dose-rate infusion of gemcitabine associated with uracil/tegafur (UFT) in patients with advanced adenocarcinoma of the pancreas.

Patients and methods: Forty-three chemotherapy-naïve patients with adenocarcinoma of the pancreas were included in this phase II study. All of whom had a Karnofsky performance status ≥50 and biimensionally measurable disease (either advanced non-resectable or metastatic); median age 59 years (range 39–77); male:female ratio 29:14. Eight patients (19%) had locally advanced disease and 35 (81%) distant metastases. Treatment consisted of gemcitabine 1200 mg/m² given as a 120-min infusion weekly for 3 consecutive weeks, plus oral UFT 400 mg/m²/day (in 2–3 doses per day) on days 1–21, cycles were given every 28 days. Measurements of efficacy included response rate, clinical benefit response, time to disease progression and overall survival.

Results: A total of 192 cycles of chemotherapy were delivered with a median of four per patient. There were two complete responses (5%) and 12 partial responses (28%), producing an overall response rate of 33% [95% confidence interval (CI) 16% to 49%]. Thirteen patients (30%) had stable disease, whereas 16 (37%) had a progression. The median time to progression was 6 months and the median overall survival was 11 months. Twenty-five patients (64%, 95% CI 47% to 78%) experienced a clinical benefit response. Grade 3–4 WHO toxicities were: neutropenia in nine patients (21%); thrombocytopenia in four (9%); anaemia in five (12%); diarrhoea in four (9%); and asthenia in one (2%).

Conclusions: A fixed dose-rate infusion of gemcitabine associated with UFT was well tolerated and showed promising activity in patients with locally advanced or metastatic carcinoma of the pancreas. This is an appropriate palliative treatment in this setting.

Key words: gemcitabine, pancreatic carcinoma, UFT

Introduction
Pancreatic carcinoma is the fifth most common cause of cancer-related death in western countries [1]. Approximately 80% of patients have non-resectable disease at diagnosis, either because of the extent of local invasion or the presence of distant metastases. There is no curative therapy for these patients.

Advanced carcinoma of the pancreas (APC) is not considered a chemo-sensitive disease. A few traditional chemotherapy drugs have demonstrated some activity; 5-fluorouracil (5-FU), cisplatin, doxorubicin, mitomycin C and the nitrosoureas. When given as single drugs or in combination, they obtain responses in 10–20% of patients, with a median survival of 4–6 months [2, 3, 4]. In spite of these poor results, two randomised trials demonstrated that chemotherapy prolongs survival by 4 months compared with supportive care [5, 6].

Gemcitabine has produced a small but significant advance in this setting. This is a pro-drug, requiring intracellular phosphorylation by the enzyme deoxycytidine kinase and
ultimately conversion to the active diFluorodeoxycytidine diphasate (dFdCDP) and triphosphate (dFdCTP) forms. The dFdCTP competes with deoxycytidine triphosphate for incorporation into DNA, which results in inhibition of DNA synthesis [7]. The dFdCDP can inhibit ribonucleotide reductase [8].

Gemcitabine, 1000 mg/m² given in 30 min every week, achieves responses in 5–15% of patients and ameliorates disease-related symptoms in 24%, with a very favourable toxicity profile [9, 10]. Higher doses may improve the results, but pharmacological studies suggest that the increment of doses given in 30 min does not increase either cytotoxicity or the therapeutic index [11, 12]. 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/m² given in 30 min [12]. Alternatively, increasing the infusion time while holding the dose rate constant at 10 mg/m²/min could result in increased intracellular levels of the active metabolites dFdCDP and dFdCTP, thus enhancing the activity of gemcitabine [13, 14]. A randomised phase II study compared two doses of gemcitabine, 2200 mg/m² given in 30 min versus 1500 mg/m² in 150 min, and both the response rate (2.7 versus 16.5%) and the 1-year survival rate (0 versus 23%) favoured the prolonged fixed dose-rate administration [15]. A pharmacokinetic analysis in this study showed higher concentrations of dFdCTP in mononuclear cells with the fixed dose-rate (336 versus 114 µM; P = 0.003).

5-Fluorouracil has frequently been used in APC. Early studies reported a 25% response rate, but this percentage has been reduced to 0–16% in more recent trials [1]. This antineoplastic activity of 5-FU is time dependent. Given as a bolus, its half life is only 15 min, so it is reasonable to think that a prolonged infusion could increase the efficacy. Given as a continuous infusion, 5-FU mainly acts by inhibiting thymidilate synthase, an enzyme involved in pyrimidine nucleotide synthesis. This mechanism suggests a possible synergism between the fluoropyrimidines and gemcitabine, because the latter inhibits deoxyxycytidine kinase, a key enzyme in the salvage pathway of pyrimidine synthesis [7]. This potential synergism has been seen in in vitro studies, where the combination had a marked cytotoxic effect against pancreatic cancer cells [16]. A phase I–II trial of gemcitabine plus 5-FU in continuous infusion obtained a response rate of 19% and a median survival of 7.4 months [17]. Although therapy with 5-FU has some advantages, the continuous infusion requires the use of an infusion pump, thereby increasing 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 plasmatic levels. This inhibition predominates in tumour cells over normal tissues, so the combination increases both the tumour concentration and antineoplastic activity of 5-FU [18, 19]. In addition, 5-FU remains in the cell for longer when given as UFT [18, 20]. In a pharmacokinetic study, UFT 370 mg/m² given orally on a 28-day schedule resulted in blood concentrations comparable to those following a continuous i.v. infusion of 5-FU 250 mg/m² [21]. These features, along with the possibility of oral administration, make UFT an interesting choice for the therapy of digestive neoplasms. However, there is limited experience with this drug in the treatment of APC. A retrospective analysis compiled the Japanese experience in a variety of tumours and reported a 25% response rate [22]. We have used the combination of gemcitabine given in 30 min, UFT and leucovorin in a previous study: the response rate was 16% and the median survival 7 months [23]. These results suggest that UFT has some activity in APC.

We designed a combination of gemcitabine given at a constant dose rate of 10 mg/m²/min plus UFT. This scheme would take advantage of the synergism between gemcitabine and the fluoropyrimidines and would be more convenient for patients. The main objective of the present study was to assess the anti-tumour activity and toxicity of this scheme in patients with APC.

**Patients and methods**

**Patient population**

From May 1999 to March 2001, 43 patients with histologically or cytologically confirmed APC entered this study. Eligible patients had: (i) locally advanced or metastatic disease not potentially curable by other therapeutic modalities; (ii) Karnofsky performance status (PS) of at least 50; (iii) estimated life expectancy of at least 12 weeks; (iv) at least 2 weeks recovery from any surgical procedure; (v) adequate bone marrow function, that is, a granulocyte count of ≥1 × 10⁹/l and a platelet count ≥350 × 10⁹/l; (vi) normal renal function, as defined by a serum creatinine level <115 µmol/l and creatinine clearance >60 ml/min; and (vii) adequate hepatic function, that is, serum bilirubin <35 µmol/l, aspartate aminotransferase and alanine aminotransferase levels <3 × the upper normal limit, unless these alterations were due to metastatic disease, in which case an increase up to 5 × 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 adequately treated basal-cell carcinoma or in situ cervical carcinoma. Patients provided written informed consent according to the directives of local ethical committees.

All patients had measurable disease, as defined by the presence of at least one lesion clearly measurable by computed tomography (CT) scan. 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: baseline Karnofsky PS <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) [24].
Table 1. Treatment scheme

| Days 1, 8 and 15 | Gemcitabine 1200 mg/m² i.v. in 120 min |
| Days 1–21     | UFT 200 mg/m²/12 h p.o.                |
| Cycles<sup>+</sup> | Every 28 days                          |

<sup>*</sup>Each patient received a minimum of three cycles, unless progressive disease was detected.

UFT, uracil and tegafur combined.

**Treatment plan**

The study regimen consisted of gemcitabine 1200 mg/m² in 120 min once weekly for 3 consecutive weeks, given through an infusion pump, and oral UFT 400 mg/m²/day (in two doses) on days 1–21. Pills were taken before meals to favour absorption (for instance, at 8 a.m. and 8 p.m.) (Table 1). Courses were repeated every 28 days for a minimum of three 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. At the end of chemotherapy, patients with stage IVA disease (T4 N0–1 M0) received radiotherapy 56–60 Gv to the pancreatic region along with weekly gemcitabine (300 mg/m²).

Toxicity for each course was recorded before the next treatment course and graded according to WHO scales [25]. Occasionally, patients suffered gastric pain related to the ingestion of UFT; as this symptom does not appear in WHO scales, we considered it to be grade 3–4 if it was intense enough to require UFT withdrawal in spite of the use of antiacids or H2-blockers. Patients were instructed to withdraw 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 the beginning of each course. Therapy was delayed for 1 week if the neutrophil count was <1.5 × 10⁹/l or the platelet count <100 × 10⁹/l on the first day of the course. Therapy was permanently discontinued if toxicity persisted after a 2-week delay. A 50% reduction in the dose of gemcitabine was used on days 8 and 15 of every course if the neutrophil count was between 1 and 1.5 × 10⁹/l or the platelet counts between 75 and 100 × 10⁹/l; the dose was skipped if lower levels were found. If the patient experienced grade 4 neutropenia or thrombocytopenia, UFT was withheld until recovery to the grade 3 level. Also, if there was grade 4 haematological toxicities, the dose of gemcitabine was reduced by 25% in subsequent courses. In the case of grade 3–4 non-haematological toxicity, the doses of gemcitabine and UFT were reduced by 25% in subsequent courses.

**Pretreatment and follow-up studies**

Patients had a full clinical history, physical examination, PS assessment, haematological and biochemical profiles (including CA 19-9 level), a chest X-ray and a CT scan of the chest and abdomen at baseline. Additional imaging investigations were performed if clinically indicated. While on the study, patients were followed weekly to assess toxicity, Karnofsky PS, analgesic consumption and pain. A blood analysis including haematological counts, serum chemistry and creatinine level was also performed weekly. A CT 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 examinations every 2 or 3 months until death.

**Toxicity and response criteria**

Toxicity for each course was recorded and graded according to WHO scales [25]. For toxicity analysis, the worst data for each patient across all courses were used. Response was evaluated by using WHO guidelines [25]. A complete response required the total disappearance of all tumours initially observed, in two observations not less than 4 weeks apart, with no evidence of new areas of malignant disease. A partial response was defined as a reduction of at least 50% in the sum of the products of the longest perpendicular diameter of all clearly measurable tumour masses, in two observations not less than 4 weeks apart, with no increase in the size of any lesion and no evidence of new lesions. Stable disease was defined as a decrease in total tumour size of <50% or a <25% increase in any measurable lesion. Progression was defined as a 25% increase in the size of any lesion, the appearance of new areas of malignant disease or PS deterioration by more than one level. 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. The 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 [10, 26]. Clinical benefit response depended on pain assessment (pain intensity and analgesic requirements), PS and weight loss. Pain was evaluated daily using the Memorial Pain Assessment Card; a positive change consisted of an improvement of 50% over baseline, and a negative change was defined as any worsening (stabilisation otherwise). A positive change in the consumption of analgesics was defined as a decrease of at least 50% in morphine-equivalent milligrams, and a negative change as any increase in the use of analgesics (stabilisation otherwise). A positive change in the Karnofsky PS was defined as an improvement of at least 20%, and a negative change as a worsening of 20% (stabilisation otherwise). A positive weight change was an improvement of at least 7%, excluding third space fluid (non-positive otherwise). 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/m² of drug given by the number of weeks elapsed from the beginning of therapy to the end of the last cycle.

The sample size was designed to reject a clinical benefit response rate <20%. According to the Fleming method [27], 19 patients were first included. As the response rate was >21%, the number of patients included was increased to 35, plus 10% to allow for losses, which gives 38 patients. 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 and the duration of response. Progression-free survival was measured from the start of chemotherapy to the date of progressive disease or death without progression.

**Results**

**Patient population**

Forty-three patients were included in the study. Table 2 outlines their features. Eight of them (19%) had extensive local infiltration at laparotomy that was considered non-resectable.
The remaining 35 patients (81%) had metastatic disease, including three patients with previously resected tumours who developed distant recurrent disease. All subjects were assessable for toxicity and response. Four patients were not assessable for clinical benefit because they had a Karnofsky PS >70 and no pain at entry.

### Treatment summary

A total of 192 cycles of chemotherapy were delivered with a median of four per patient (range one to nine). Five patients received seven or more courses. Five patients received less than three courses: four had progressive disease, whereas the other decided to drop from the study after the first course. All patients were included for response and survival calculations on an intention-to-treat basis.

The median dose intensity of UFT was 1848 mg/m²/week and that of gemcitabine was 765 mg/m²/week, which corresponded to 88 and 85% of the planned doses, respectively. Weekly doses of gemcitabine were reduced by 25% in 10 patients and doses of UFT in 13. Gemcitabine on days 8 or 15 was skipped in 16% of the courses. Few days of treatment with UFT were skipped (either because of the patient’s toxic reactions or noncompliance). Of 192 courses of UFT, 14 courses (7%); four patients) were interrupted for 1–7 days and 21 courses (11%); five patients) had therapy interrupted for >7 days.

### Response and survival

Response data are listed in Table 3. Two patients (5%) obtained a complete response and 12 (28%) had a partial response, for an overall response rate of 33% [95% confidence interval (CI) 16% to 49%]. Three of these responses appeared after the fourth course of chemotherapy. Thirteen patients (30%) had stable disease and 16 (37%) had a progression. The median duration of response was 7.5 months. Four out of eight patients with locally advanced disease responded (50%), as compared with eight out of 35 (23%) with metastatic disease (P = 0.4 difference not significant). Response was not related to the location of metastases or the percentage of weight loss. Of note, 41% of patients with a Karnofsky PS ≥80 responded, compared with 26% of those with a Karnofsky PS <70; this difference was not significant (P = 0.52), possibly because of the small sample size. The median time to progression was 6 months, and the median overall survival 11 months. The median survival for responding patients has not been reached after a median follow-up of 12 months. The median survival for non-responding patients was 7 months. The 1-year actuarial survival rate was 32%.

### Clinical benefit

Thirty-nine patients had symptoms at entry. Twenty-six patients had a low Karnofsky PS at entry: 12 (46%) improved, whereas eight (31%) remained stable and six (23%) worsened (Table 4). Thirty-five patients had a baseline pain intensity score of at least 20 mm: 20 (57%) improved without increasing analgesia, seven (20%) remained stable and eight (23%) worsened. Thirty-eight patients consumed >10 morphine-equivalent milligrams of analgesics at entry: 11 (29%) reduced the consumption, 16 remained stable and 11 (29%) increased the consumption. Twenty-one patients had significant weight loss at entry: 13 patients (33%) experienced a weight gain of at least 10%, 17 (44%) remained stable and nine (23%) lost weight. As a whole, 25 patients (64%; 95% CI 47% to 78%) had a clinical benefit response.

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### Table 2. Patients’ characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>29 (67%)</td>
</tr>
<tr>
<td>Female</td>
<td>14 (33%)</td>
</tr>
<tr>
<td>Median age, years (range)</td>
<td>59 (39–77)</td>
</tr>
<tr>
<td>Karnofsky performance status</td>
<td></td>
</tr>
<tr>
<td>100–80</td>
<td>17 (40%)</td>
</tr>
<tr>
<td>70–70</td>
<td>26 (60%)</td>
</tr>
<tr>
<td>Pain score, range</td>
<td></td>
</tr>
<tr>
<td>0–19</td>
<td>8 (19%)</td>
</tr>
<tr>
<td>20–49</td>
<td>16 (37%)</td>
</tr>
<tr>
<td>50–100</td>
<td>19 (44%)</td>
</tr>
<tr>
<td>Weight loss</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>3 (7%)</td>
</tr>
<tr>
<td>1–10%</td>
<td>19 (44%)</td>
</tr>
<tr>
<td>&gt;10%</td>
<td>21 (49%)</td>
</tr>
<tr>
<td>Disease at presentation</td>
<td></td>
</tr>
<tr>
<td>Locally advanced</td>
<td>8 (19%)</td>
</tr>
<tr>
<td>Metastatic disease</td>
<td>35 (81%)</td>
</tr>
<tr>
<td>Sites of metastatic disease</td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>29 (82%)</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>8 (22%)</td>
</tr>
<tr>
<td>Lung</td>
<td>5 (14%)</td>
</tr>
<tr>
<td>Peritoneum</td>
<td>4 (11%)</td>
</tr>
<tr>
<td>Others</td>
<td>4 (11%)</td>
</tr>
</tbody>
</table>

### Table 3. Therapeutic results in 43 patients

<table>
<thead>
<tr>
<th>Results</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>Partial response</td>
<td>12 (28%)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>13 (30%)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>16 (37%)</td>
</tr>
</tbody>
</table>
Toxicity

All 43 patients were evaluable for toxicity (Table 5). The chemotherapy regimen was well tolerated, the main side effects being gastrointestinal and haematological. No toxic deaths were recorded. Grade 3–4 toxicities were as follows: neutropenia in nine patients (21%), with one case of febrile neutropenia; anaemia in five (12%; all grade 3); thrombocytopenia and diarrhoea in four each (9%); and asthenia in one (2%). Grade 1–2 side effects were: nausea/vomiting in 32% of patients; neutropenia in 35%; diarrhoea and asthenia in 25% each; transitory elevation in transaminases in 14%; and skin rash in 7%. Four patients (9%) had a mild flu-like syndrome consisting of myalgia, arthralgia and fever. Two patients (5%) required hospitalisation for complications related to the treatment; one due to grade 4 diarrhoea and the other because of febrile neutropenia.

Discussion

Advanced pancreatic carcinoma is associated with the poorest 5-year survival of all gastrointestinal malignancies. Although two recent randomised trials suggest that chemotherapy improves survival and quality of life in these patients [5, 6], the effect is small [4]. Most studies of chemotherapy have yielded disappointing results, with objective responses in about 15% of cases and overall survival rates of 6–7 months.

New chemotherapeutic regimens have been developed recently to improve these results by exploiting synergism between gemcitabine and other drugs, such as cisplatin and 5-FU. In two recent phase II trials combining cisplatin and gemcitabine, the response rates varied between 11 and 31% and the median survival between 8 and 10 months [28, 29]. The preliminary results of a trial that compared cisplatin and gemcitabine with gemcitabine alone suggest that the combination increases both the response rate (31 versus 10%) and the clinical benefit (45 versus 38%) [30]. With regard to the combination of gemcitabine and 5-FU, some phase II trials showed promising results with response rates of 20%, improvement in disease-related symptoms in 45–65% of patients and median survival time of 10 months [17, 31]. However, two randomised studies that compared this combination with gemcitabine alone, did not demonstrate any improvement in survival [32, 33]. In a phase III trial, gemcitabine was compared with gemcitabine–5-FU (bolus administration), and the median survival was 5.4 and 6.7 months, respectively.
However, the progression-free survival was longer in the combination arm [31]. In the other study, a randomised phase II trial, gemcitabine was compared with gemcitabine–5-FU (continuous infusion) and, again, the response rate (9% and 13%, respectively) and the overall survival (6 months in both groups) were the same [33]. Further randomised studies are needed to establish the efficacy of this combination.

One study combined gemcitabine with cisplatin, 5-FU (in continuous infusion) and epirubicin, in 59 patients. A response was recorded in 51% of them, 78% had a clinical benefit and the median survival was 10 months. However, toxicity was high, with 85% of patients suffering grade 3–4 neutropenia [34]. Gemcitabine is also being combined with other drugs, such as oxaliplatin, docetaxel and irinotecan. Response rates range from 10% to 29% and the median survival from 6 to 10 months [35–37].

In the present trial, we tried to achieve the best results of gemcitabine and a fluoropyrimidine. Gemcitabine was optimised through the use of a fixed dose-rate of 10 mg/m²/min, whereas the schedule for administration of UFT tried to simulate the effects of a continuous infusion of 5-FU. The response rate was 33%, the median survival 11 months and the clinical benefit rate 64%. As our patients had an unfavourable prognostic profile (81% with metastatic disease and 60% with Karnofsky PS <80), these relatively good results observed in our trial could be due to the use of a fixed dose-rate of gemcitabine. Little is known about such a strategy for the treatment of APC or other tumours [38, 39]. In a randomised phase II trial performed in patients with APC, the fixed dose-rate was superior in terms of response rate (16.6 versus 2.7%) and 1-year survival (23% versus 0) [15]. However, in another trial, in which gemcitabine 1500 mg/m² at a fixed dose-rate was combined with bolus 5-FU, a 17% response rate and a median survival of 6 months were reported. Haematological toxicity was very high and 68% of patients did not receive the planned doses, which could have limited the efficacy of that regimen [40]. On the other hand, the superiority of a continuous infusion of 5-FU over the bolus administration has been demonstrated in colorectal tumours, but not in APC. However, two phase II studies reported response rates of 16% and 21%, with a prolonged infusion in patients with APC, which suggests some increased activity [41, 42].

As therapy for APC is palliative, toxicity and convenience for the patient are important issues in addition to efficacy. Our patients mainly suffered haematological side effects, although of mild degree. This toxicity is attributable to the dose of gemcitabine. We selected the dose level immediately below that of the maximum tolerated dose found in a phase I trial (1500 mg/m² as a fixed dose-rate) [15]. With that maximum tolerated dose, Tempero et al. described grade 4 neutropenia and thrombocytopenia in 25% and 58% of courses, respectively, so we decided to decrease the dose by one level because UFT would be added. Our regimen was well tolerated, 21% and 9% of patients having grade 3–4 neutropenia and thrombocytopenia, respectively. Although 9% also had diarrhoea. On the other hand, oral fluoropyrimidines avoid the cost and inconveniences of infusion pumps, thus reducing interference with daily life.

In summary, the combination of a fixed dose-rate of gemcitabine and UFT is well tolerated and showed a promising activity in the treatment of APC. It is an appropriate palliative therapy in this setting. Given the synergism between cisplatin, gemcitabine and the fluoropyrimidines [43], we have begun a phase II study with the combination of cisplatin, gemcitabine and UFT.

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