Front-line treatment of inoperable or metastatic pancreatic cancer with gemcitabine and capecitabine: an intergroup, multicenter, phase II study

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Received 22 June 2003; revised 24 September 2003; accepted 7 October 2003

Purpose: To evaluate the efficacy and toxicity of gemcitabine (GEM) combined with capecitabine (CAP) in untreated patients with inoperable or metastatic pancreatic cancer.

Patients and methods: Fifty-three patients with pancreatic cancer (85% stage IV) were enrolled. Patients were treated with GEM 1000 mg/m² on days 1 and 8 and CAP 1300 mg/m² per day PO (per os), divided into two equal doses on days 1–14, in 21-day cycles.

Results: In an-intention-to-treat analysis, 10 (18.9%) objective partial responses were achieved (95% confidence interval 8.33% to 29.4%). Twenty-two (42%) patients had stable disease and 15 (28%) had progressive disease. The median response time was 3 months (range 1.5–7.0) and the median time to tumor progression was 6.5 months (range 3.5–15.5). Median overall survival time was 8 months (range 1.0–15.5) and 1-year survival was 34.8%. Pain improvement during treatment was observed in 23 of 43 (53%) patients, and eight of 18 (44%) patients who had been receiving opioids discontinued their use. Weight gain was observed in 12 of 33 (36%) patients. Grade 3 anemia occurred in five (9%) patients and grade 3–4 thrombocytopenia occurred in three (6%). Grade 3–4 neutropenia occurred in 13 (25%) and five (9%) patients, respectively, and two (4%) developed febrile neutropenia. Non-hematological toxicity was mild.

Conclusion: In patients with pancreatic cancer, the combination of GEM with CAP is an active and well tolerated regimen that merits further evaluation in prospective randomized studies.

Key words: capecitabine, gemcitabine, pancreatic cancer

Introduction

Gemcitabine (GEM) monotherapy is considered to be the standard treatment for inoperable and metastatic pancreatic cancer, improving overall survival (OS) and offering a statistically significant clinical benefit over the best supportive care; however, the overall objective response rate still remains low [1, 2]. Over recent years, several studies have introduced new combination regimens with or without GEM; some combinations have demonstrated a higher or similar response rate and survival to those of GEM monotherapy [3–11]. A randomized study comparing single agent GEM versus GEM plus 5-fluorouracil (5-FU) has been published [12] and other studies are ongoing, but a new active treatment for metastatic pancreatic cancer has not yet been established [12]. Therefore, for the time being, clinical research is open to trials using new combinations.

One of the active drugs against pancreatic cancer is 5-FU, which has also been used in combination with other drugs in phase II studies [13, 14]. Capecitabine (CAP), a new fluoropyrimidine with the advantage of oral administration, has recently been introduced into clinical practice. CAP is metabolized in both the liver and tumor cells into 5-FU, resulting in high intratumoral 5-FU concentrations. Moreover, CAP can be substituted for the continuous 5-FU infusion [15–17]. The main adverse reactions of CAP are diarrhea and hand-foot syndrome, although hematological toxicity is quite limited [17]. At a dose of 2500 mg/m² daily, myelotoxicity is of low grade as opposed to bolus i.v. administration of 5-FU [17].

Phase II studies of CAP administration in patients with metastatic pancreatic cancer revealed an overall response rate of 9.5%, while 41% of the patients experienced stable disease; in addition, clinical benefit could be demonstrated in 24% of patients [18]. The combination of GEM and CAP seems attractive since the drugs have a different mechanism of action and non-overlapping toxicity; furthermore, the combination is convenient since one of
the drugs is orally administered. This combination has already been evaluated in phase I studies and the recommended dose for further phase II studies is 650 mg/m² b.i.d. At the dose level of 800 mg/m² b.i.d., two of six patients experienced dose-limiting toxicities [19, 20].

The Gastrointestinal Working Parties of the Hellenic Oncology Research Group (HORG) and the Hellenic Cooperative Oncology Group (HeCOG), decided to conduct an intergroup, multicenter, phase II trial in order to evaluate the efficacy and tolerance of the GEM–CAP combination in previously untreated patients with inoperable locally advanced and metastatic pancreatic cancer.

Patients and methods

Patients >18 years of age with histologically or cytologically confirmed adenocarcinoma of the pancreas and bidimensionally measurable disease, and who were chemotherapy- and radiotherapy-naïve, were enrolled in the study. Other eligibility criteria included a World Health Organization (WHO) performance status (PS) of 0–2, life expectancy of at least 3 months, adequate bone marrow reserves (granulocyte count ≥1500/µl, platelet count ≥120 000/µl), normal renal (serum creatine concentration <1.2 mg/dl) and liver function tests (total serum bilirubin concentration <3 mg/dl provided that serum transaminases and serum proteins were normal), normal cardiac function of reconstituent by clinician unstable angina pectoris or myocardial infarction, or congestive heart failure within the previous 6 months, and no central nervous system involvement. Prior surgery was allowed if it had taken place at least 3 weeks before. Patients with active infection, malnutrition or a second primary tumor (except for a non-melanoma skin epithelioma or in situ cervix carcinoma) were excluded from the study. All patients gave their written informed consent to participate in the study.

Treatment

All patients were treated on an outpatient basis. GEM (Gemzar®; Eli Lilly, Indianapolis, IN) was given as a 30 min i.v. infusion on days 1 and 8 of each cycle at a dose of 1000 mg/m². CAP (Xeloda®; Hoffman La Roche Laboratories) was administered orally at a dose of 1300 mg/m² per day, divided into two equal doses, for 14 consecutive days followed by 1 week of rest. Cycles were repeated every 21 days provided that patients had recovered sufficiently from the drug-related side-effects. Standard ondansetron anti-emetic treatment was administered to all patients. Prophylactic administration of recombinant human granulocyte colony-stimulating factor (rhG-CSF) was not allowed. Patients with grade 3 granulocytopenia received subsequent cycles with rhG-CSF (Granocyte®; Aventis Pharma, Collegeville, PA) support (150 µg/m² s.c. from days 9–15 inclusive). Treatment was administered for at least six cycles or until disease progression, at the physicians’ discretion. The protocol was approved by the Ethical and Scientific Committees of the participating hospitals.

Dose adjustment criteria were based on hematological parameters. In cases of grade 3 or 4 afebrile neutropenia, subsequent cycles were repeated with rhG-CSF prophylactic administration, as above. In cases of febrile neutropenia or grade 3 or 4 neutropenia, despite the prophylactic administration of rhG-CSF, GEM and CAP doses were reduced by 25%. In cases of grade 3 or 4 thrombocytopenia lasting for <5 days, the doses of both drugs were reduced by 25%. The dose of CAP was reduced by 25% in case of grade 3 or 4 diarrhea or hand-foot syndrome. Toxicities were graded according to WHO guidelines [21].

Patient evaluation

Pretreatment evaluation included complete medical history and physical examination, full blood cell count including differential leukocyte and platelet count, a standard biochemical profile (and creatinine clearance when necessary), serum carcinoembryonic antigen (CEA), and CA 19.9 determinations, electrocardiogram, chest X-rays, ultrasound of the upper abdomen, and computed tomography (CT) scans of the chest, upper and lower abdomen. Additional imaging studies were performed upon clinical indication. Full blood counts with differential were performed weekly; in case of grade 3 or 4 neutropenia or grade 4 thrombocytopenia, full blood counts with differential were evaluated daily until the absolute granulocyte count was >1000/µl and the platelet count was >75 000/µl. A detailed medical and physical examination was completed before each course of treatment in order to document symptoms of the disease and treatment toxicities. Biochemical tests, ECG, serum CEA and CA 19.9 determinations, and chest X-rays were performed every 6 weeks and a neurologic evaluation was performed by clinical examination. Lesions were measured after each cycle if they were assessable by physical examination or by chest X-rays; lesions assessable by ultrasound or CT scans were evaluated after three chemotherapy cycles.

Definition of response

Complete response (CR) was defined as the disappearance of all measurable or evaluable disease, signs and symptoms and biochemical changes related to the tumor for at least 4 weeks, during which time no new lesions may appear. Partial response (PR) was defined as >50% reduction in the sum of the products of the perpendicular diameters of all measurable lesions compared with pretreatment measurements, lasting for at least 4 weeks, during which time no new lesions may appear and no existing lesions may enlarge. For hepatic lesions, a reduction of >30% in the sum of the measured distances from the costal margin at the midclavicular line and at the xiphoid process to the edge of the liver was required. Stable disease (SD) was defined as <50% reduction and a <25% increase in the sum of the products of the two perpendicular diameters of all measured lesions and the appearance of no new lesions for 8 weeks. Progressive disease (PD) was defined as an increase in the product of the two perpendicular diameters of any measurable lesion by >25% over the size present at entry into the study, or, for patients who responded, the size at the time of maximum regression and the appearance of new areas of malignant disease. Bilirubin increase without recovery after endoscopic retrograde cholangiopancreatography (ERCP) or stent set was considered as disease progression. A two-step deterioration in performance status, a >10% loss of pretreatment weight or increasing symptoms did not by themselves constitute progression of the disease; however, the appearance of these complaints was followed by a new evaluation of the extent of the disease [17]. All responses had to be maintained for at least 4 weeks and be confirmed by an independent panel of radiologists.

Assessment of clinical benefit

The assessment of pain relief was based on both the consumption of analgesics (narcotics and non-narcotics) and the patient’s own evaluation of pain using a scale graded from 0 (no pain) to 10 (maximum pain necessitating narcotics for relief). A >50% decrease in analgesic consumption with no need for narcotics, coupled with the patient’s evaluation of a >50% decrease in pain intensity, was characterized as ‘pain improvement’. A 50% increase in the administration of analgesics, in combination with the patient’s evaluation of a 50% increase in pain intensity, was characterized as ‘pain deterioration’. All other cases were characterized as ‘no change’. Symptoms of vomiting and diarrhea were assessed according to the number of daily episodes: a >50% decrease in number was characterized as ‘improvement’, whereas a >50% increase was characterized as ‘deterioration’. All other cases were characterized as ‘no change’. Patients were also asked to grade their fatigue and anorexia using a scale of 0 (no
patients [n = 45 (85%)] had stage IV disease. Four (7.5%) patients had undergone surgery (all for biliary decompression) due to jaundice, and at enrollment were considered inoperable; these patients were enrolled in the study after their bilirubin level fell below 2 mg/dl. The majority of patients had a moderate or low grade adenocarcinoma. At enrollment, 43 (81%) patients had pain, 35 of whom were receiving analgesics; 18 (51%) of these patients were also treated with opioids. At the beginning of treatment, 29 (55%) patients had weight loss (<5 kg during the previous 3 months).

Compliance with treatment

A total of 304 chemotherapy cycles were administered with a median of six cycles per patient (range from one to 15). The median interval between cycles was 22 days (range 21–29). Median dose intensity for GEM and CAP was 611 mg/m^2/week (range 303–667) and 5460 mg/m^2/week (range 2410–6067), corresponding to 92% and 90% of the planned protocol dose, respectively. Fifty-nine (19%) cycles were delayed from 3 to 43 days (median 7 days) due to hematological toxicity (14 cycles with grade 3 or 4 neutropenia), non-hematological toxicity (one cycle), and both hematological and non-hematological toxicity (one cycle); moreover, 43 cycles were delayed for reasons unrelated to the treatment (late admission, imaging evaluation, patient’s request for personal reasons). Dose reduction was necessary in 29 (9.5%) cycles because of toxicity (hematological, 15 cycles; non-hematological, 14 cycles). Four (7.5%) patients refused to continue treatment because of toxicity (hematological, 15 cycles; non-hematological, 14 cycles). Four (7.5%) patients refused to continue treatment after the first cycle. At the time of this analysis, 22 (41.5%) patients are alive and 31 (58.5%) are dead. The causes of death were disease progression (30 patients) and upper gastrointestinal bleeding due to anticoagulant therapy of a deep venous thrombosis (one patient).

Responses to treatment and survival

Responses were analyzed on an intention-to-treat basis. There were no complete responses. Out of 53 patients, there were 10 (18.9%; 95% CI 8.33% to 29.4%) partial responses at all sites of the disease. Twenty-two (41.5%) patients had stable disease and 15 (28%) had progressive disease. Sites of tumor responses were the pancreas in nine of 48 patients (19%), the liver in eight of 15 (28%) had progressive disease. Sites of tumor responses were the pancreas in nine of 48 patients (19%), the liver in eight of 15 (28%) and the lymph nodes in three of 19 (16%) patients. There were no responses in lung or peritoneal metastatic lesions. In the eight patients with inoperable stage III disease, there were no partial responses; all objective responses were documented in patients with stage IV disease: objective responses were documented in three out of 19 (16%) patients with a PS of 0, and in seven out of 34 patients (21%) with a PS of 1 and 2. The median duration of response was 3 months (range 1.5–7.0) and the median time to tumor progression was 6.5 months (range 3.5–15.5). Median OS time was 8 months (range 1.0–15.5) and 1-year survival was 34.8%. Overall median survival for stage III disease (n = 8 patients) was 10 months (95% CI 6.68% to 13.32%; range 1–15.5) and for stage IV, 8.0 months (95% CI 6.0% to 10.0%; range 1–15) (P = 0.769; log-rank test).

Increased pretreatment serum CA 19.9 levels were available in 28 (58%) of 48 evaluable patients. The levels of CA 19.9 were

Table 1. Patients’ characteristics

<table>
<thead>
<tr>
<th>Patients enrolled (n)</th>
<th>53</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>65</td>
</tr>
<tr>
<td>Range</td>
<td>42–78</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>28 (53)</td>
</tr>
<tr>
<td>Female</td>
<td>25 (47)</td>
</tr>
<tr>
<td>Performance status (WHO), n (%)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>19 (36)</td>
</tr>
<tr>
<td>1</td>
<td>33 (62)</td>
</tr>
<tr>
<td>2</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Stage of disease, n (%)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>8 (15)</td>
</tr>
<tr>
<td>IV</td>
<td>45 (85)</td>
</tr>
<tr>
<td>Histologic grade, n (%)</td>
<td></td>
</tr>
<tr>
<td>Well differentiated</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Moderate differentiation</td>
<td>19 (36)</td>
</tr>
<tr>
<td>Low differentiation</td>
<td>7 (13)</td>
</tr>
<tr>
<td>Unclassified</td>
<td>24 (45)</td>
</tr>
<tr>
<td>Primary location (dominant), n (%)</td>
<td></td>
</tr>
<tr>
<td>Head of pancreas</td>
<td>27 (51)</td>
</tr>
<tr>
<td>Body of pancreas</td>
<td>8 (15)</td>
</tr>
<tr>
<td>Tail of pancreas</td>
<td>6 (11)</td>
</tr>
</tbody>
</table>

fatigue or anorexia) to 10 (maximum fatigue or anorexia). A 50% decrease or increase in symptom intensity indicated ‘improvement’ or ‘deterioration’, respectively.

Statistical design

This was an extended, two-step, phase II study. According to the trial design, 30 patients were to be enrolled during the first part of the trial and if an objective response rate of <15% was achieved, the treatment would have been abandoned; otherwise, 20 additional patients were to be enrolled. The primary end point of the study was the efficacy of the regimen, and the secondary end points were OS and tolerance. Duration of response was calculated from the day of the first demonstration of response until progressive disease. The time to tumor progression (TTP) was calculated from the day of entry into the study until documented PD. OS was calculated from the day of enrollment until death. The median probability of survival and the median TTP were estimated by the Kaplan–Meier method; confidence intervals for response rates were calculated using methods for the exact binomial confidence interval (CI). Comparison of variables was performed using the χ² test.

Results

Patients’ demographics

From April 2001 until June 2002, 53 patients (28 male) were enrolled in this intergroup, multicenter trial; patient characteristics are shown in Table 1. Median age was 65 years (range 42–78). Performance status was as follows: 19 (36%), 33 (62%) and one (2%) patient(s) had a PS of 0, 1 and 2, respectively. Most of the
Table 2. Response rate by site of disease [n (%), total n = 53]

<table>
<thead>
<tr>
<th>Site</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreas</td>
<td>48</td>
<td>9</td>
<td>22 (46)</td>
<td>17 (35)</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>19</td>
<td>3</td>
<td>9 (47)</td>
<td>7 (37)</td>
</tr>
<tr>
<td>Liver</td>
<td>29</td>
<td>8</td>
<td>10 (34)</td>
<td>11 (38)</td>
</tr>
<tr>
<td>Lungs</td>
<td>9</td>
<td>–</td>
<td>4 (44)</td>
<td>5 (56)</td>
</tr>
<tr>
<td>Peritoneum</td>
<td>5</td>
<td>1</td>
<td>2 (40)</td>
<td>2 (40)</td>
</tr>
<tr>
<td>Other</td>
<td>15</td>
<td>1</td>
<td>2 (40)</td>
<td>2 (40)</td>
</tr>
</tbody>
</table>

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

decreased or remained at pretreatment levels in 11 (39%) and eight (29%) patients, respectively. Conversely, CA 19.9 serum levels were increased in 10 patients.

PS changes and control of symptoms

Nineteen and 33 patients had a PS of 0 and 1, respectively. Four (21%) patients with a PS of 0 had a decrease in PS (2) at the end of the six cycles of chemotherapy, while the remaining patients showed no significant changes in PS. Among the 33 patients with PS 1, one (3%) showed improvement (PS 0) while 10 (30%) experienced a deterioration in PS (eight patients with PS 2 and two patients PS 3). The remaining 22 patients showed no change in PS.

Forty-three (81%) patients suffered from pain at enrollment; pain improvement during treatment was observed in 23 (53%) patients, while pain intensity increased in three (7%) patients. In 17 (39.5%) patients, pain intensity remained unchanged during the whole treatment period. Thirty-five (66%) patients were under analgesic treatment at enrollment, 18 (51%) of whom were receiving opioids. A complete discontinuation or a >50% decrease in the consumption of analgesics was observed in 11 (31%) and six (17%) patients, respectively. Eight (44%) out of the 18 patients who had been receiving opioids at enrollment completely discontinued their use.

Fatigue was present in 34 (64%) patients at enrollment. Improvement was reported by 11 (32%) and deterioration by three (9%) patients. There was no change in fatigue intensity in the remaining patients. Four patients had diarrhea at enrollment; improvement of diarrhea was observed in two patients while no change was reported by the remaining two. Thirty-three (62%) patients reported weight loss when enrolled. During treatment, 12 (36%) reported weight gain of >5 kg, while weight loss increased in seven (21%) patients. Body weight remained stable in the remaining patients.

Toxicity

All patients were evaluable for toxicity (Table 2). Grade 3 anemia occurred in five (9%) patients who required transfusion of nine packed red blood cell units. Fourteen (26%) additional patients with grade 2 anemia were treated with recombinant erythropoetin. Grade 3 and 4 thrombocytopenia occurred in one (2%) and two (4%) patients, respectively. No patient required hospitalization for the treatment of a hemorrhagic episode or platelet transfusions. Thirteen (25%) and five (9%) patients presented with grade 3 and 4 neutropenia, respectively. Two (4%) patients developed febrile neutropenia (duration 2–7 days) and both required hospitalization. Both patients recovered uneventfully. Recombinant human G-CSF was administered in 44 chemotherapy cycles due to grade 3–4 neutropenia. Non-hematological toxicity was relatively mild (Table 3). Grade 2–3 fatigue was reported by 11 (21%) patients. Grade 2–3 diarrhea occurred in seven (13%), skin eruption in two and oedema in seven (13%) patients. One patient developed grade 2 hand-foot syndrome. Seven (13%) patients developed non-neutropenic infections, two of whom required hospitalization for between 2 and 11 days. All patients were treated uneventfully with broad-spectrum antibiotics.

Discussion

The results of the present study seem to indicate that the combination of GEM and CAP is a relatively active and well tolerated regimen for the treatment of patients with pancreatic cancer. Indeed, the 18.9% objective response rate, which corresponds to 10 partial responses, and the 8 months overall median survival are acceptable for this poor-prognosis malignant disease. Single-agent GEM therapy has shown marginal objective activity in patients with pancreatic cancer and the drug is now considered the treatment of choice for this disease based on improvement of quality of life and the clinical benefit in a high percentage of patients [1, 2].

To date, published data concerning the combination of GEM and CAP in pancreatic cancer are sparse. Preclinical studies based on a xenograft model indicated the synergistic activity of CAP and GEM [22]. Hidalgo et al. [4] reported promising results in a phase I/II study of GEM and continuous 5-FU infusion in patients with pancreatic cancer; indeed, the observed objective response rate was 19.2%, with a median progression-free survival of 7.4 months. Recently, Hess et al. [19] reported a phase I/II clinical trial of the GEM–CAP combination. These authors indicated that the doses
recommended for phase II studies were GEM 1000 mg/m² given on days 1 and 8 and CAP 650 mg/m² b.i.d. for 14 consecutive days of a 21-day cycle. In 27 patients with measurable disease, they observed one complete and four partial responses for an overall response rate of 18.5%, which is similar to that observed in the present study.

In this study, the combination of GEM and CAP also had an important effect on the serum levels of CA 19.9 and patients’ symptoms. The combination of the two drugs resulted in a >50% decrease in serum levels of CA 19.9 in 39% of the patients. Other studies have shown that a decrease in the tumor marker CA 19.9 can identify patients who benefit from the treatment [19, 23]. Halm et al. [24] reported that patients with a >20% drop in CA 19.9 levels during the first 8 weeks of treatment had a significantly longer median survival than patients with a rise or a decrease of <20%. The clinical benefit associated with the GEM–CAP combination was also demonstrated by our observations, as follows: (i) pain intensity was decreased in 53% of the patients, and eight of the 18 patients who had been receiving narcotic analgesics before treatment discontinued use afterwards; (ii) 36% of the patients experienced weight gain during treatment, whereas 32% of the patients suffering from fatigue experienced improvements in this symptom; and (iii) the median survival of the patients was 8 months, which is among the longest observed in similar studies. It is also interesting to note that 35% of the patients, even with stage IV disease, survived for >1 year. No clinical or laboratory differences could be detected in this subset of patients with longer survival when compared with other patients of a similar disease stage who showed no response to treatment and who had a short survival. Moreover, no difference in survival between locally advanced disease and metastatic disease was observed in our patients. All of these observations clearly indicate that the combination of GEM and CAP is a relatively active regimen against inoperable locally advanced and metastatic pancreatic cancer. Similar findings were presented in a recently published study where patients were randomized for treatment with GEM alone or in combination with CAP. The monotherapy group showed an objective response rate of 14%, while in the combination group it was 17%. This difference was not found to be significant [25].

The toxicity of the GEM and CAP combination was well tolerated and was mainly associated with myelosuppression. Comparing the toxicity profile with other studies, no major differences were found. The non-hematological toxicity of the GEM–CAP regimen was mild, with grade 3 toxicity occurring in <5% of the patients. It is of interest to note that the incidence of hand-foot syndrome was very low since only one patient developed it (grade 2). Hess et al. [19] observed no hand-foot syndrome in their phase I/II study. The low incidence of skin toxicity observed in both studies may be attributed to the low dose of CAP.

In conclusion, the combination of GEM with CAP is an active regimen for patients with pancreatic cancer, rendering an 18.9% objective response rate, which is higher than that achieved by each of the drugs alone. This combination is associated with an improvement in tumor-related symptoms in a substantial proportion of patients and with an acceptable median survival. In addition, the regimen not only has a favorable toxicity profile, it is also more convenient for the patient. Therefore, this regimen, as compared with GEM monotherapy, merits further evaluation in a prospective randomized phase III study.

References