Abstract. Background: Gemcitabine is an active agent in pancreatic cancer, showing clinical synergy with 5-fluorouracil (5-FU). The aim of the study was to evaluate the safety and efficacy of the combination of gemcitabine and 5-FU in patients with advanced adenocarcinoma of the pancreas. Patients and Methods: Forty-two patients (median age, 62 years), with advanced or metastatic pancreatic adenocarcinoma, were enrolled in the study. The combination of gemcitabine (1000 mg/m²) and 5-FU (600 mg/m²) was administered on days 1, 8 and 15 and repeated every 28 days. Results: A total of 168 cycles (median 4 cycles per patient) were administered. Partial responses were observed in 6 patients (14.2%) and stable disease in 11 (26.2%). The overall clinical benefit was 40.4%. Symptom relief and improvement of performance status were observed in 18 (42.8%) patients. The median time to progression, median duration of response and the median overall survival, were 6, 7 and 13 months, respectively. The most common grade 3 to 4 toxicities were neutropenia, anaemia and diarrhoea. Conclusion: The combination of gemcitabine and 5-FU is an active regimen for the treatment of advanced pancreatic cancer with an acceptable toxicity profile.

Cancer of the pancreas is a particularly aggressive disease, with few reports of 5-year survivors. Adenocarcinoma of the pancreas, the most common histological type, has a median survival of 9-12 months and an overall 5-year survival rate of 3% for all stages (1, 2). Cure can only be achieved if the primary tumour can be radically resected, but over 50% of patients have clinically apparent metastatic disease at the time of diagnosis. Among patients whose disease is considered to be resectable, 50% will die of recurrent tumour within 2 years. This is mainly due to the aggressiveness of the disease and the current lack of effective systemic therapies. Therapy for metastatic disease remains palliative. Few agents, based mainly on 5-FU regimens, have demonstrated activity of >10%. Moreover, most of the reported series have been small, and not all encouraging results have been duplicated (3-5).

On the basis of a randomised trial comparing gemcitabine with 5-fluorouracil (5-FU), which highlighted the superiority of gemcitabine in terms of median and 1-year survival, gemcitabine has replaced 5-FU as the first-line choice for the treatment of advanced pancreatic carcinoma (6). Due to its palliative potential, gemcitabine has become the standard of care for patients with unresectable pancreatic adenocarcinoma. Gemcitabine is a nucleoside analogue requiring conversion to the active di- and tri-phosphate forms of fluoro deoxycytidine to cause DNA chain termination (7, 8). There is in vitro and in vivo evidence to suggest that the combination of gemcitabine and 5-FU is synergistic. The inhibition of thymidylate synthase by 5-FU may be assisted in depleting pyrimidine nucleotides by gemcitabine that functions by inhibiting deoxycytidine kinase, an enzyme involved in the salvage of pyrimidines.

A number of other combinations based on gemcitabine have been assessed, including: flutamide, tamoxifen, marimastat, cisplatin, oxaliplatin, docetaxel, epirubicin, irinotecan and others (9-17). Few combinations have proven superior to that of single agent gemcitabine, with response rates rarely exceeding 20% (18-26).

The aim of this study was to evaluate the activity and the toxicity profile of the combination of gemcitabine and 5-fluorouracil for metastatic or locally advanced inoperable pancreatic adenocarcinoma.

Key Words: Pancreatic cancer, gemcitabine, 5-FU.
Patients and Methods

Patient selection. Patients with locally advanced or metastatic histologically confirmed pancreatic adenocarcinoma and no prior chemotherapy were enrolled in the study. The eligibility criteria were adequate bone marrow, hepatic and renal functions. Patients aged 18 to 75 years, with a Karnofsky performance status (PS) of between 100-50, and with a life expectancy of more than 3 months were eligible. All patients had measurable disease, as defined by the presence of at least one lesion clearly identified by computed tomography (CT) scan. Pleural effusion, ascites, osteoblastic lesions or previously irradiated lesions were not accepted as measurable disease.

The exclusion criteria were: prior treatment with either of the study drugs, prior radiation to any of the areas of measurable or evaluable disease, active secondary malignancy, psychiatric or addictive disorders, and pregnancy or lactation.

The study was performed according to the Good Clinical Practice (GCP) guidelines and the Declaration of Helsinki. Approval was obtained from all local ethical boards, and written informed consent was obtained from all patients.

The primary end-point of this open label phase II trial was the overall response rate (CR + PR), and the secondary end-points were time to progression (TTP), survival, toxicity and symptom relief.

Treatment plan. Patients received gemcitabine (1000 mg/m$^2$) as a 30-minute intravenous (i.v.) infusion, and 5-FU (600 mg/m$^2$) by i.v. push on days 1, 8 and 15. The treatment was repeated every 4 weeks. Responding patients (CR, PR and SD) continued to receive the regimen until progression, the appearance of unacceptable toxicity, or patient refusal. Prophylactic granulocyte colony-stimulating factor (G-CSF) was not routinely used. Adequate treatment for control of pain and other symptoms were allowed and were recorded in detail during the study.

Criteria for response and toxicity evaluation. At study entry all patients received a physical examination, ECG, Karnofsky performance status, full blood count, liver and kidney function tests and urinalysis. Chest X-ray (and a CT scan if indicated), CT scan of the abdomen and pelvis, bone scan if indicated and bone radiographs (following abnormal bone scan) were obtained within 3 weeks prior to study entry. Objective tumor assessments were repeated following cycle 3, following clinical signs indicative of disease progression, at the end of treatment and every 3 months until disease progression.

Karnofsky criteria were used to define the response and performance status (PS). Toxicity was evaluated according to the National Cancer Institute (NCI) Common Toxicity Criteria (27). All documented side-effects were included.

The duration of response (DR) was defined as: the number of days from the date of first documented response to the earlier of a) death (from any cause) or progression, and b) the last on-study tumour assessment. Time to tumour progression was estimated from the date of the first course to the first evidence of disease progression. For the purposes of overall clinical benefit (OCB), patients were assessed if they had obtained a complete (CR), partial response (PR) and or maintained stable disease (SD). Clinical benefit depended on pain assessment (pain intensity and analgesic requirements), PS and weight loss, which were recorded at each visit and evaluated according to established criteria (28). Pain assessment was based on the Memorial Brief Pain Assessment Card (29). A positive pain change consisted of an improvement of 50% over baseline, and a negative as any worsening. 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. 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%. A positive weight change was an improvement of at least 7%. Patients with a clinical benefit response had an improvement in one or more of these parameters for at least 4 weeks, without worsening in any of the others.

Statistical analysis. Statistical analysis was performed using the statistical package of SPSS version 10.07. All tests were two-sided; p < 0.05 was considered significant. Continuous data were summarized using descriptive statistics; they are presented as means, medians or proportions where appropriate, with 95% confidence intervals. All patients were analyzed for safety.

Results

Patient characteristics. Forty-two patients were enrolled in this study; all were evaluable for response and toxicity. The patient characteristics are listed in Table I. The median age was 62 years (range 38-75 years). Thirty-five (83.3%) patients had metastatic disease and the remaining 7 (16.6%) had unresectable locally advanced disease.

Treatment. A total of 168 cycles of chemotherapy were delivered with a median of 4 per patient. Eighteen cycles were delayed for 1 week due to toxicity, 6 cycles were delayed on day 1, 7 on day 8 and 5 on day 15.
Response and survival. Among the 42 patients eligible for response evaluations, 17 patients demonstrated OCB (40.4%), including 6 PR (14.2%), and 11 patients with SD exceeding 6 months. The median duration of response was 7 months (range 3-12 months). One out of 5 patients with locally advanced disease obtained a partial remission and 2 remained stable, while 5 out of 37 patients with metastatic disease obtained a partial remission and 9 remained stable.

Clinical benefit. Chemotherapy was combined with adequate pain treatment. All 17 of the OCB patients required less pain medication at the end of chemotherapy and demonstrated improved appetite and improved PS. Forty patients had symptoms at entry. Eighteen had PS 100-80 and 26 PS 70-50. Symptom relief and improvement in PS was observed in 17 (40.4%) patients (Table II).

Toxicity. The major toxicities are listed in Table III. Grade 3/4 neutropenia was observed in 4 patients (9.5%), who were treated with G-CSF, and no patient was hospitalized with febrile neutropenia. None of the 9 patients, who developed grade 1 or 2 neutropenia, received prophylactic G-CSF. Slight rises in transaminase levels (grade 1/2) were recorded in 4 patients, while 5 patients experienced chills and fever. Grade 3/4 events included anaemia in 5 (12.0%) and diarrhoea in 3 (7.1%) patients. There were no treatment-related deaths.

Discussion

The majority of regimens used to treat pancreatic cancer have only shown small increases in survival and quality of life above those of best supportive care. In general, all the regimens have been disappointing with median survival rarely exceeding 6 months, and response rates of less than 20% (28-31). The results from a phase III trial demonstrated that, to date, no combination chemotherapy utilizing 5-FU is superior to 5-FU alone (26).

Of the new chemotherapeutic agents, only gemcitabine has proven superior to 5-FU. Much was expected following the transition to gemcitabine monotherapy (12-14, 31, 32). Recent studies, including one by Scheithauer et al., investigating biweekly high-dose gemcitabine alone or in combination with capecitabine, have questioned whether or not gemcitabine’s addition to a fluoropyrimidine will prove superior to single-agent gemcitabine (32). This latest trial reconfirms the results of many combinations (17-26) that have suggested monotherapy with gemcitabine is superior to combinations containing 5-FU, or indeed gemcitabine plus 5-FU.

Alternative combinations that appear to be synergistic include the gemcitabine/platinum combinations. Following on from some encouraging results in phase II trials, a recently published phase III trial indicated response rates of 25% (25). The authors demonstrated a statistically significantly longer median time to disease progression of 8 vs. 20 months for gemcitabine vs. gemcitabine plus cisplatin, and a superior response rate of 9.2% vs. 26.4%, respectively. Although neither the clinical benefit nor median overall survival was improved in the combination arm of this trial that randomized only 107 patients, it was suggested that the gemcitabine plus cisplatin regimen warrants further investigation.

The combination of gemcitabine and 5-FU has demonstrated favourable data suggesting that it was slightly superior to single-agent gemcitabine (5, 12-14), without compromising the toxicity profile of gemcitabine. However, a phase III trial comparing gemcitabine in combination with 5-FU versus gemcitabine alone concluded that the addition of 5-FU to gemcitabine did not improve the median survival of patients, and that trial resources should address other combinations (26). One of the main difficulties in clarifying whether there is superior efficacy with combination therapies is the trial population sizes: the majority of data were ascertained from small phase II studies, all of which concluded that a more concerted international effort is needed.

We report that the combination of gemcitabine and 5-FU is an active regimen for the treatment of advanced pancreatic cancer and is associated with mild toxicity. As
metastatic pancreatic carcinoma is incurable, the anticipated risks of chemotherapy, which are often substantial, must be balanced against the gains that may be achieved. Therefore, new combinations and treatment regimens still need to be assessed against single-agent gemcitabine in patients with advanced disease. No study, to date, has demonstrated results encouraging enough to lead the field in another direction, other than possibly poly-combination(s). Effective treatment regimens are still needed for this rapidly debilitating disease; new drugs, sequential schedules and more radical combinations may need to be investigated.

References


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