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Clinical report

Phase II study of gemcitabine in combination with cisplatin in patients with locally advanced and/or metastatic pancreatic cancer

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The present phase II trial was performed to assess the efficacy and toxicity of polychemotherapy with gemcitabine and cisplatin in patients with locally advanced or metastatic carcinoma of the pancreas. Sixteen patients received six courses of an i.v. cytotoxic regimen consisting of gemcitabine (1000 mg/m^2, days 1, 8 and 15) and cisplatin (35 mg/m^2, days 1, 8 and 15) administered in 28-day intervals. Complete remission (CR) occurred in one patient (6%), partial remission (PR) in four patients (25%) and stable disease in seven patients (44%), whereas four patients (25%) developed progressive disease resulting in an overall response rate of 31%. Mean duration of responses (CR+PR) was 3.6 (range 0.7–8.5) months and mean time to progression was 7.4 (range 3.8–12.6) months. After a mean observation period of 11.5 months the overall survival was 9.6 months with 12 patients (75%) still being alive, which compares favorably with historical data of the administration of gemcitabine alone. The performance status improved in three (19%) and stabilized in eight (50%) out of 16 patients for 4 weeks or longer. Treatment-associated toxicity included alopecia of WHO grade III in all cases, leukopenia of WHO grades I and II in 10 patients (63%), grade III in five patients (31%), and thrombocytopenia grades I and II in four patients (25%), and grades III and IV in 10 patients (63%). We conclude that the administered dosage and schedule of gemcitabine and cisplatin in patients with locally advanced or metastatic cancer of the pancreas constitutes an active cytotoxic regimen associated with moderate toxicity. [© 2000 Lippincott Williams & Wilkins.]

Key words: Chemotherapy, cisplatin, gemcitabine, pancreas.

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Introduction

More than 80% of patients with cancer of the pancreas are diagnosed either with locally advanced or distant disease which makes them ineligible for radical surgical resection. The median survival time of locally advanced disease is 6–10 months and 3–6 months in metastatic disease, resulting in an overall 5-year survival of less than 5%.[1] A small number of cytotoxic drugs including 5-fluorouracil (5-FU),[2] cisplatin[3] and epirubicin[4] have been shown to exert modest activity in pancreatic cancer. Although the combination of 5-FU (500 mg/m^2) and radiotherapy at a dose of 20 Gy in the adjuvant setting has significantly raised the median survival from 10.9 to 21 months (results of the GITCCG),[5] new agents are obviously needed to improve prognosis for locally advanced and metastatic disease. One of these agents with increased activity resulting in improved clinical benefit response has been shown to be gemcitabine (difluorodeoxycytidine), which is an analog of cytosine arabinoside and a pyrimidine antimetabolite of well-characterized metabolism and cytotoxic activity.[6,7] The dose-limiting toxicity of gemcitabine lies in its myelosuppressive potential with thrombocytopenia occurring more frequently than granulocytopenia.[8] Recent phase I and II trials of gemcitabine have established 1250 mg/m^2/week to represent a well-tolerated and moderately toxic dose.[9–11] The drug has undergone considerable testing in various malignancies, and exhibited particular activity in pancreatic cancer, non-small cell lung cancer, advanced breast cancer and cisplatin-refractory ovarian carcinoma.[12–15]

The initial observation of good efficacy of gemcitabine in pancreatic cancer has led to several clinical trials with the drug administered at a dose of 800–1500 mg/m^2 on days 1, 8 and 15 in a 28-day cycle.[11,16,17] Furthermore, a phase II study of gemcitabine in 5-FU-resistant patients[18] resulted in a response rate (RR) of 10.5% and a median overall survival (OS) of 15 weeks. A controlled randomized study comparing the efficacy of gemcitabine administered in a weekly dose of 1000 mg/m^2 versus 5-FU showed significantly better results for gemcitabine concerning clinical benefit (24 versus 5%, p=0.002), median survival (5.7 versus 4.4 months, p=0.003) and 12-month survival (18 versus. 2%).[15] In trials of polychemotherapy including gemcitabine, the addition of epirubicin resulted in an overall RR of 23% and a median survival time of greater than 5.5 months.[19] After observing a synergistic effect in preclinical models of gemcitabine and cisplatin,[20] a small randomized phase II study comparing gemcitabine (1000 mg/m^2 weekly $\times 7$) monotherapy with polychemotherapy including gemcitabine (1000 mg/m^2) and cisplatin (25 mg/m^2) was performed which resulted in better results obtained in the polychemotherapy versus the monotherapy arm (RR: 42 versus 10%; clinical benefit: 55 versus 57%).[21]

In the present investigation, we administered a combination of gemcitabine with cisplatin to patients with locally advanced or metastatic cancer of the pancreas within the frame of a phase II trial. We report about the good efficacy of the combination concerning overall RR (31%), improvement or stabilization of performance status (69%) and overall survival (9.6 months). Considering its moderate toxicity, a larger phase III trial testing for the efficacy of polychemotherapy with gemcitabine and cisplatin in locally advanced or metastatic cancer of the pancreas seems warranted.

Patients and methods

Patients

The study was initiated in February 1997 as a phase II trial and included 16 patients (eight females and eight males) with a mean age of 56 years (range 33–72). All patients suffered from locally advanced and/or metastatic, histologically verified carcinoma of the pancreas. All patients were evaluable for efficacy and toxicity of the chosen therapeutic protocol. Histological examination showed adenocarcinoma in 15 patients (histopathologic grade 1 in two patients, grade 2 in four patients, grade 3 in five patients, n.o.s. grades in four patients) and neuroendocrine carcinoma of the pancreas in one patient. Twelve patients had received no prior chemotherapy, whereas the remaining four patients had received prior chemotherapy consisting of 5-FU-containing regimens. Patient characteristics are shown in Table 1. The current report covers a mean observation period of 11.5 months (range 3–21).

Inclusion criteria

Inclusion criteria consisted of histologically verified locally advanced (not amenable to surgery of curative intent) and/or metastatic carcinoma of the pancreas at the time of diagnosis, Eastern Cooperative Oncology Group (ECOG) performance status of $\leqslant 2$ (ambulatory and capable of self care), age 19–80 years, creatinine clearance $\geqslant 30$ ml/min, a signed patient consent to participate in the study, clinically measurable disease, defined as bidimensionally measurable lesions of at least 1 cm $\times$ 1 cm, as defined by CT or MRI scan.

Further inclusion criteria were: estimated life expectancy $\geqslant 12$ weeks, patient compliance and geographic proximity that allowed adequate follow-up, adequate bone marrow reserve, defined by white blood cell count (WBC) $\geqslant 3.0 \times 10^9$/l, absolute neutrophil count (ANC) $\geqslant 1.5 \times 10^9$/l, platelets $\geqslant 100 \times 10^9$/l, hemoglobin $\geqslant 9.0$ g/dl, and finally the ability to understand the nature of the study and to give written informed consent. Childbearing potential was either terminated by surgery, radiation or menopause, or attenuated by use of an approved contraceptive method (IUD), birth control pills or barrier device during and for 3 months after trial.

Table 1. Patient characteristics (n=16)

	N
Females/males	8/8
Mean age stab range	56 (33–72)
Histology	
adenocarcinoma	15
neuroendocrine	1
Locally advanced disease	2
Metastatic disease	14
Site of metastases	
liver	9
lymph nodes	5
Prior chemotherapy	4
ECOG status	
0	5
1	8
2	3

Exclusion criteria

Exclusion criteria consisted of previous treatment of the current disease with more than one chemotherapeutic regimen and/or radiotherapy, local disease amenable to surgery of curative intent, metastases to the skeleton only, inadequate hematologic function (as defined by WBC $< 3.0 \times 10^9$/l, granulocytes $< 1.5 \times 10^9$/l platelets $< 100 \times 10^9$/l), the staging procedure being carried out more than 2 weeks before onset of chemotherapy, second malignancy with the exception of *in situ* cervix cancer or adequately treated basal cell or squamous cell carcinoma of the skin, history of atrial or ventricular arrhythmias and/or history of congestive heart failure (even if medically controlled), history of clinical and electrocardiographically documented myocardial infarction, and pre-existing motory or sensory neurotoxicity above grade 1 according to WHO criteria (severe paresthesia and/or mild weakness or worse). Finally, active infection or any other serious underlying medical condition which would impair the ability of the patient to receive protocol treatment, altered mental status that would prohibit the understanding and giving of informed consent, pregnancy and breast feeding, severe hepatic dysfunction (bilirubin and/or transaminases $\geqslant 2.5$ times upper limits of normal) and creatinine clearance < 30 ml/min.

Cytotoxic therapy

Dose and schedule. This was a prospective open-label study of gemcitabine in combination with cisplatin in patients with advanced pancreatic cancer. Gemcitabine (1000 mg/m^2 body surface) was given by a 30-min continuous infusion subsequently followed by a 1-h infusion of cisplatin (35 mg/m^2 body surface) on days 1, 8 and 15 of a 28-day cycle. This combination has been shown to be safe in previous investigations.[21]

Supportive therapy. Standard antiemetic medication, including 5-HT$_3$-antagonists and dexamethasone, was administered. Hydration was carried out as indicated.

Evaluation of patients. Before treatment was started, patients were staged according to the TNM classification for pancreatic cancer. The following procedures were furthermore performed in all patients: physical examination, chest X-ray, laboratory tests, biopsy (pancreas and/or metastatic lesion), abdominal CT or MRI scan and total body bone scan.

Hematologic and non-hematologic toxicities as well as ECOG performance status were assessed on each treatment day. In order to evaluate response rates, a complete obligatory radiologic work-up was performed every other treatment cycle. The same assessment method used to determine the disease status at baseline (CT or MRI scan) was used consistently for evaluation of efficacy throughout the study.

Duration of therapy. After the documentation of clinical complete remission (CR), two additional cycles of cytotoxic chemotherapy were administered. In case of stable disease (SD) or partial remission (PR), a total of six cycles was given.

Documented progression of disease according to WHO criteria resulted in discontinuation of the treatment protocol.

Objectives

The primary objective was to determine the objective RR in patients with locally advanced or metastatic histologically verified carcinoma of the pancreas. Secondary objectives were to evaluate duration of response, time to disease progression and OS. According to WHO criteria, therapy-related hematologic and non-hematologic toxicity as well as ECOG performance status were evaluated (see Evaluation of patients).

Statistical analysis

Statistical calculations were done by the log-rank test (overall survival) performed with the BMDP-PC program package using a level of significance of 0.05.

Results

Patients

Sixteen patients were treated with a total of 78 courses of gemcitabine and cisplatin. A median number of 6 (range 2–9) cycles was administered. In addition, standard antiemetic medication was given.

Toxicity

The most common toxicity was myelosuppression with thrombocytopenia grades III and IV occurring in 10 patients, respectively. Five patients developed leukopenia grade III, whereas anemia grade III was seen in five patients. Results of toxicity are detailed

in Table 2. None of the patients discontinued therapy due to adverse effects and no toxic death occurred.

Response rates

CR occurred in one patient (6%), whereas four patients (25%) experienced PR and seven patients (44%) SD. Four patients (25%) developed PD while under therapy. Thus, the overall RR (CR+PR) was 31% (five of 16). After administering a total of 78 cycles, the clinical benefit was 75% (12 of 16). Out of the four assessable patients who received prior chemotherapy, two patients experienced SD, whereas two patients progressed. Mean response duration was 3.6 (range 0.7–8.5) months, in case of CR 8.5 months. Patients with PR had a mean response duration of 3.35 (range 2.0–6.1) months and the mean duration of SD was 3.6 (range 1.9–6.5) months. Mean time to progression was 7.4 (range 3.8–12.6+) months.

Performance status during treatment

Among 11 patients with ECOG performance status 1 and 2, improvement of the performance status of a duration of 4 weeks or more occurred in three (27%) patients. In addition, stabilization of the performance status for 4 weeks or more during treatment was achieved in eight (50%) out of 16 patients.

Survival

Overall survival was 9.6 months with 12 patients (75%) still being alive after a mean observation period of 11.5 (range 3–21+) months. A Kaplan–Meier plot is presented in Figure 1.

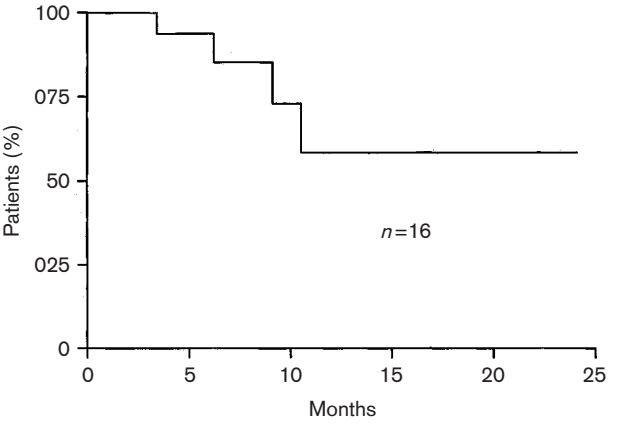

Figure 1. Survival curve (OS) of 16 patients with locally advanced and/or metastatic pancreatic cancer under polychemotherapy with gemcitabine and cisplatin.

Table 2. Hematologic toxicity of polychemotherapy with gemcitabine and cisplatin in 16 patients with locally advanced and/or metastatic pancreatic cancer (no. of patients)

WHO Grade	Thrombocytopenia	Leukopenia	Anemia
0	2 (12.5%)	1 (6.3%)	0
1	2 (12.5%)	2 (12.5%)	4 (25.0%)
2	2 (12.5%)	8 (50.0%)	7 (43.8%)
3	5 (31.3%)	5 (31.3%)	5 (31.3%)
4	5 (31.3%)	0	0

Table 3. Responses to polychemotherapy with gemcitabine and cisplatin in 16 patients with locally advanced and/or metastatic pancreatic cancer

CR	6% ($n=1$)
PR	25% ($n=4$)
SD	44% ($n=7$)
PD	25% ($n=4$)

Discussion

In the present trial, we report on the efficacy and toxicity of a polychemotherapy regimen consisting of gemcitabine and cisplatin in locally advanced and/or metastatic pancreatic carcinoma. The activity of mono- and polychemotherapy in the palliative treatment of advanced and/or metastatic pancreatic cancer is generally poor: currently, gemcitabine appears to be the most active single agent for the treatment of pancreatic cancer (RR: 5.4–11%; OS: 5.6–6.3 months)[15,16,22] associated with an acceptable toxicity profile.[23] Previous trials combining cisplatin with 5-FU and epirubicin or etoposide have shown RRs of 12–20% with a median OS of 6.2–11 months.[24–27] Recent trials using gemcitabine and 5-FU produced a RR of 13–33% and an OS of 5.5–8 months accompanied by moderate toxicity.[28–31] In continuation of preclinical models demonstrating a synergistic effect of gemcitabine and cisplatin,[20] subsequent studies evaluating this combination regimen led to a RR of 11.5–36% and an OS of 7.4–8.3 months.[32–34] Furthermore, Villa *et al.*[35] reported a RR of 69% and an OS of 8 months using a chemotherapeutic regimen containing cisplatin/epirubicin/gemcitabine/5-FU. Thus, polychemotherapy under the inclusion of gemcitabine clearly shows superior results over the use of gemcitabine alone.

In the present study, this assumption could be further corroborated, as polychemotherapy with

gemcitabine and cisplatin resulted in a RR of 31%. More importantly, among 11 patients with ECOG performance status of 1 and 2, an improvement occurred in three (27%) and stabilization of performance status in eight (50%) out of 16 patients for 4 weeks or more during treatment. Furthermore, 75% of patients were alive after 11.5 months after diagnosis with an OS of 9.6 months at this timepoint. Thus, our data compare favorably with other reports of phase II trials using gemcitabine and cisplatin[32–34] for the treatment of patients with advanced and/or metastatic pancreatic cancer. The favorable responses to polychemotherapy were accompanied by low to moderate toxicity, thus justifying the initiation of randomized phase III trials which very likely would lead to the identification of new standard treatment with both gemcitabine- and cisplatin-containing polychemotherapeutic regimens for patients with locally advanced and/or metastatic pancreatic cancer.

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