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ORIGINAL ARTICLE

First-line treatment of pancreatic cancer patients with the combination of 5-fluorouracil/folinic acid plus gemcitabine: a multicenter phase II trial by the CONKO-study group

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Abstract
Purpose This open-label, multi-center phase II study investigated the efficacy and safety of the combination of 5-fluorouracil (5-FU)/folinic acid (FA) plus gemcitabine (GFF) in patients with advanced pancreatic cancer. The study is based on our completed dose finding phase I trial.
Methods A total of 90 patients (pts) were recruited between 02/2000 and 04/2002 to receive 5-FU 750 mg/m^2 (24 h, i.v.), FA 500 mg/m^2 (2 h, i.v.) and gemcitabine 1,000 mg/m^2 (30 min, i.v.) on days 1, 8, 15, and 22. Treatment was repeated on day 43 until disease progression. The primary objective was the 1-year survival rate. The trial was conducted in compliance with the Declaration of Helsinki.
Results The 1-year survival rate was 25% [95% CI: 16–34], median overall survival was 6.8 months [95% CI: 5.13–8.45], 9 patients showed partial responses (PR) so that the overall response rate was 10.3%. Overall control rate (PR + stable disease for at least 6 months) was 56%. Median time to progression was 4.6 months [95% CI: 3.68–5.52]. In 402 GFF cycles, we observed adverse events grade 3 in up to 10% of patients and grade 4 below 5% of patients.
Conclusions The GFF combination appears to be effective and well tolerated. This intravenous regimen represents an intensified therapy with low frequency of toxicities and seems to be convenient for patients who are unable to get oral anti-neoplastic medication. After these encouraging results, the German CONKO-002 trial investigated the GFF regimen versus single-agent gemcitabine.

Keywords Pancreatic cancer · 5-FU · Folinic acid · Gemcitabine · Chemotherapy

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Introduction

Adenocarcinoma of the pancreas is a highly aggressive cancer type, characterized by early local spread, extensive invasion, precocious metastasis and nearly total chemoresistance. In spite of intensive research in the last decade, the 5-year survival rate in advanced disease is still less than 5% [1]. At present, pancreatic cancer is the fourth most frequent cause of death from solid tumors in the Western world [2]. Besides rapid disease progression, patients with advanced pancreatic cancer (APC) suffer from merged collateral symptoms including abdominal pain, nausea and emesis, inability of natural nutrition intake, taste abnormalities, early satiety, and fatigue. These additional

symptoms contribute substantially to degradation in performance and quality of life [3, 4].

Gemcitabine (GEM), the standard first-line chemotherapy for pancreatic cancer in the last decade, generates modest improvement of tumor-related symptoms and a marginal survival advantage [5]. A lot of chemotherapeutic combinations and targeted agents have been studied in several trials to increase the efficacy in the treatment of pancreatic cancer [6, 7]. Hitherto only the combination of GEM and erlotinib in first-line therapy has been found superior to single-agent GEM in selected patients [8]. Further therapy beyond progression of first-line treatment was offered to patients with stabilized performance status, the phase III proved treatment option with oxaliplatin/folinic acid, and 5-fu (OFF) can be considered as reference regimen [9].

The classic nucleotide analogue 5-fluorouracil (5-FU) has been intensively studied in several doses and combinations but has failed to have a real impact in patients with APC [10, 11]. While a 24-h 5-FU infusion setting was shown to be effective in other solid cancers, the combination of it with GEM had not been studied before our treatment design. Thus, this phase II study investigates the efficacy and safety of GFF in first-line treatment of advanced pancreatic cancer. The regimen is based on encouraging findings in the phase I trial conducted by the CONKO-study group [12].

Materials and methods

Patients with histologically proven pancreatic cancer, advanced inoperable disease, and measurable lesions were eligible for the study. The other eligibility criteria were age 18–75 years, Karnofsky Performance Status $\geq$60%, estimated life expectancy of at least 3 months, adequate renal (serum creatinine $\leq$1.5 mg/dl) and liver function (serum bilirubin $<1.5 \times$ upper normal limit (UNL); ALT and AST $\leq 2.5 \times$ UNL or $\leq 5 \times$ UNL in cases of liver metastasis) and adequate bone marrow reserve (leukocytes $\geq$3.5/nl, platelet count $\geq$100/nl). Exclusion criteria were as follows: prior chemotherapy/radiotherapy, severe heart disease (NYHA IV or myocardial infarction in the last 4 weeks), severe active infection, pregnant or breast feeding women, inadequate contraception, known dihydropyrimidine dehydrogenase deficiency, metastases involving the central nervous system, severe neurological impairment or mental disorder, active concomitant malignancy or other malignancy (except carcinoma in situ) in the past 5 years or any other serious medical conditions interfering with the study conditions. All patients had to give their informed consent before study intervention. Period of recruitment was from 01/2000 till 05/2002. The study was approved by the institutional review board at each center and was conducted in accordance with the Declaration of Helsinki (October 1996, Somerset West). The trial registration identifier is NCT00919282.

Study design and treatment

The trial was designed as an open-label, single-arm, multicenter, phase II study conducted to investigate the efficacy and safety of the GFF regimen in patients with APC. GEM 1 g/m^2 was administered as a 30-min intravenous infusion, followed by intravenous administration of folinic acid 0.5 g/m^2 over 2 h. Directly thereafter, 5-FU was intravenously administered at a dose of 750 mg/m^2 over 24 h. Weekly outpatient treatment for 4 weeks was followed by 2 weeks of rest and was resumed in week 7. Patients remained on treatment until disease progression or a patient's refusal. Any further treatment after disease progression was left to the discretion of the treating physician.

Dose-adjustment criteria were based on hematological parameters and on the severity of non-hematological toxicities. If bone marrow suppression is detected, combination therapy was modified or suspended according to the following criteria: leukocyte count 0.75–1.0/nl or platelet count 75–100/nl give 75% of the full dose. Leukocyte count 0.5–0.75/nl or platelet count 50–75/nl give 50% of the full dose. Leukocyte count $<$0.5/nl or platelet count $<$50/nl hold the dose. The worsening by one degree in non-hematological parameters except alopecia or fatigue led to an adjustment of 75%, by two degrees to an adjustment of 50%. Adverse events were graded according to the National Cancer Institute (NCI) Common Toxicity Criteria (CTC) scale (version 2.0).

Pretreatment and follow-up study

Before study entry, patients presented their complete medical histories and underwent physical examination. A complete blood count with differential testing was performed, and electrolyte and creatinine levels were measured. Biochemical tests and urinalysis were performed. Electrocardiograms, chest X-rays and computed tomography (CT) scans of the abdomen were taken at baseline in all patients within 4 weeks before starting treatment. Additional imaging investigations (CT-scan of chest or head, bone scintigraphy) were performed if clinically indicated or for further disease measurement. Patients were followed up until death.

Assessment of efficacy and safety

CT/MRI scanning of measurable disease to assess tumor response took place at least every two cycles according to

the WHO Response Criteria in Solid Tumors. All responses (partial response/complete response) had to persist for at least 4 weeks and be confirmed by an independent panel of radiologists. Analysis of efficacy was performed in the intent-to-treat populations. The intent-to-treat population was defined to include all patients who received at least one dose of GFF. Analysis of safety was performed in the safety population, which was defined to include all patients who received at least one dose of GFF. Safety and tolerability were assessed by monitoring adverse events according the NCI (National Cancer Institute) CTCAE (Common Terminology Criteria of Adverse Events) 2.0. A complete blood count with differential testing was performed on every treatment day; serum chemistry, creatinine and electrolyte levels were determined in each cycle. In cases of severe toxicities, blood tests were performed more frequently.

Statistical analysis

The primary endpoint of this study was the 1-year survival (1-YS) rate. Secondary endpoints were median overall survival (mOS) and median time to progression (mTTP), response rate (RR) and side effects (SE).

The 1-YS rate was 18% in a previous major phase III study of single-agent GEM in patients with APC [5]. Therefore, the threshold rate of 1-YS for the GFF regimen was set at 18%. The 1-YS rate was to be at least 25% to be interesting for further phase III testing. We set the needed number of cases on 90 patients to ensure a sufficient outcome.

Overall survival was calculated from start of treatment until death or last contact in cases of lost to follow-up. TTP was measured from start of treatment until any significant sign of disease progression (CT/MRT or new non-measurable lesion, e.g. ascites) or last contact in cases of lost to follow-up. RR was calculated by the ratio of responding patients to the whole cohort.

The 1-YS rate, mOS, and the mTTP were estimated using the Kaplan–Meier method. Confidence intervals (CI) for response rates were calculated using methods for the exact binomial confidence interval. Duration was specified in months (30.5 days = one month). The statistical evaluation was based on SPSS 13.0.

Results

Ninety consecutive patients were recruited in this multicenter trial. Two patients withdrew from informed consent before first infusion. The remaining 88 patients were included in the safety and intent-to-treat analysis. Patient characteristics are shown in Table 1. The mean age was 61 [range 30–81] years. Locally advanced disease was found in 19 (22%) and metastatic disease in 69 patients (78%). The most common metastatic sites were the liver and the peritoneum.

Table 1 Patient characteristics

Characteristics	*n*
Recruited patients	90
Excluded patients	2
Sex	
Male	58 (66%)
Female	30 (34%)
Age (years)	
Median	61
Range	30–81
Disease extension	
Locally advanced	19 (22%)
Metastatic	69 (78%)
Site of metastasis	
Liver	65 (74%)
Lung	12 (14%)
Peritoneum	15 (17%)
Other	7 (8%)

No complete response to GFF was observed. Nine patients (10%) with confirmed partial responses were documented in the intent-to-treat population ($n = 88$). Sixty-two patients (71%) were stabilized for longer than 3 months and 16 pts (18%) for longer than 12 months. Seventeen patients (19%) had a progressive disease within the first 3 months in the intent-to-treat (ITT) population. The overall control rate (PR + stable disease for at least 6 months) was 56% (Table 2).

The median progression free survival (PFS) was 4.6 months [95% CI: 3.68–5.52]. The median OS time was 6.8 months [95% CI 5.13–8.45], and the 1-YS rate was 25% [95% CI: 16–34] (Fig. 1).

Table 2 Response of treatment

Response	$n = 88$
Complete response	0 (0%)
Partial response	9 (10%)
Stable disease	62 (71%)
3–6 months	22 (25%)
>6–9 months	18 (21%)
>9–12 months	6 (7%)
>12 months	16 (18%)
Progressive disease (within first 3 months)	17 (19%)

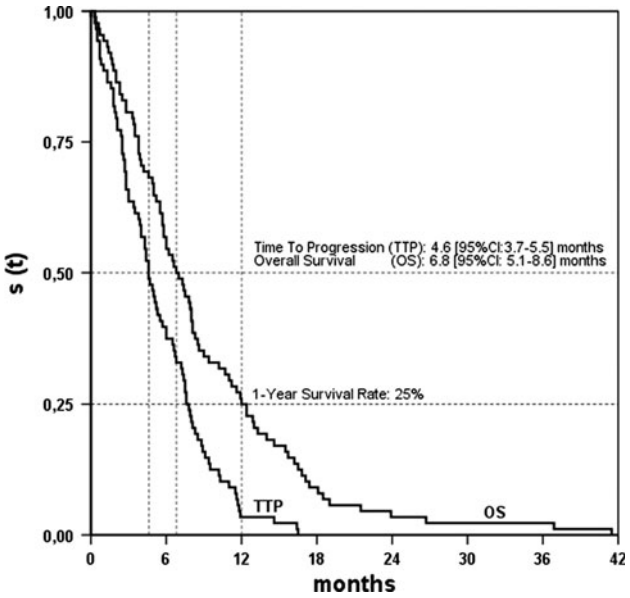

Fig. 1 Kaplan–Meier estimation of overall survival and time to progression

Subfindings

The median OS time was 7.5 months (95% CI: 4.94–10.01) for locally advanced disease and 6.6 months (95% CI: 4.87–8.3) for metastatic disease; this was not statistically significant ($p = 0.291$). Gender was an interesting parameter, but did not significantly influence overall survival (female: 8.0 months [95% CI: 6.52–9.48]; male 6.0 months [95 CI: 4.63–7.37], $p = 0.241$) or time to progression (female: 5.1 months [95 CI: 2.42–7.78]; male 4.3 months [95% CI: 3.02–5.58]; $p = 0.163$). Age did not correlate with overall survival. Younger patients in our study did not have a higher expectation of survival than older patients.

Adverse events

Patients received a total of 402 cycles of chemotherapy (median 4.0 cycles, range 1–13). For safety, 88/90 patients were evaluated. The average dose intensity was 93% [33–100%] of the planned dose schedule. There were no worst thrombosis or infection of the venous port system which leads to therapy interruption or venous port system ex-plantation. Up to 60% of port systems were not eligible for blood sucking methods while time of therapy. Commonly observed adverse events during chemotherapy are shown in Table 3. Thrombocytopenia grades 3 and 4 occurred in 10 and 1%, respectively; leucopenia grade 3 was detected in 10%. No patient suffered from grade 4 leucopenia. Nausea/emesis grade 3 occurred in 6% and grade 4 in 1% in spite of prophylactic anti-emetic treatment. No patient developed febrile neutropenia. No hand-foot syndrome was observed.

Table 3 Adverse events (NCI CTC 2.0)

Adverse events	Grade 3 *n* (%)	Grade 4 *n* (%)
Anemia	5 (6)	1 (1)
Leucopenia	9 (10)	0 (0)
Thrombocytopenia	9 (10)	1 (1)
Bilirubin	4 (5)	3 (3)
AST	3 (3)	1 (1)
Alkal Phosphatase	6 (7)	1 (1)
Creatinine	0 (0)	0 (0)
Fever	0 (0)	0 (0)
Nausea/vomiting	5 (6)	1 (1)
Hand-foot-syndrome	0 (0)	0 (0)

There were no significant correlations between occurrence of toxicities and gender ($p = 0.413$), age ($p = 0.247$) or stage ($p = 0.891$).

Discussion

The study evaluated the efficacy of the combination of GEM and 5-FU modulated by folinic acid. The primary objective of the study was the 1-YS rate because survival is a more definitive target point than the response rate or time to progression, which are both influenced by different methods of measurement and subjective evaluations.

The 1-YS rate was 25%, thus scratching the preplanned efficacy end point (at least 25% was needed to be of interest in further treatment) and reaching the same range as the Gemcitabine-Erlotinib combination (Moore). Older pts do not have worse outcome due to combined therapy regimen with GFF. The addition of 5-FU/FA did not produce more toxicity, but the infusion required a central vein access via the venous port system. The patients accepted the venous port system very well, and many appreciated it later as access for the home based parenteral nutrition support or individual pain management.

GEM in combination with fluoropyrimidines has been widely used in several studies [11]. The setting of a 24-h 5-FU infusion modulated with folinic acid was examined by EORTC (GastroIntestinal Tract Cancer Cooperative Group), but efficacy turned out to be only marginal with an overall survival of 4.3 months in 37 patients [13].

Two phase II trials using a similar GEM regimen as we did but an increased 5-FU dose (2 g/m^2) for the 24 h-infusion, resulted in the same duration of survival and response but produced grade 3 and 4 toxicities at incidences well above 10% [14, 15]. When in the trial of the Spanish Cooperative Group for GI tumor therapy, the 5-FU

dose was increased up to 3 g/m^2 and GEM up to 1.4 g/m^2, the 1-YS rate was also 25%, but there were much more side effects, with grade 3 and 4 haematological toxicities in up to 45% of the patients [16]. Our regimen turned out to work along the fine line between efficacy on the one hand and quality of life deterioration due to chemotherapeutic side effects on the other.

At least two large phase III trials with 5-FU as bolus [17] or long-lasting continuous infusion [18] failed to be more efficacious than GEM alone. Also the combination of GEM with continuous oral capecitabine had no more impact on overall survival than GEM alone [19, 20].

There exist meta-analyses for several anti-drug combinations [6, 19], which showed survival benefit favors the combined therapy strategy. It is up to the oncologist to choose the best benefit/risk calculation for the individual patient depended from main characteristics like age, performance status, tumor stage and other.

Based on the encouraging phase II results, we conducted the CONKO 002 phase III trial, to investigate the GFF regimen versus the standard therapy. The results of the CONKO 002 trial were already presented at the ASCO meeting in 2005 [21]. Subfindings for patients with good performance status demonstrated survival benefit when undergoing combined therapy, but there was no overall survival advantage estimated [21]. These data are not published in full setting at this time. Therefore, we presented this results relatively late after completing our phase II trial to offer this infusional regimen (without oral medication part) for patients who suffer from gastrointestinal obstruction, nausea and emesis, side effects like diarrhea or are not able to get or dislike oral medication.

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Conflict of interest The authors declare that they have no competing interest or financial disclosures.

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