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Best supportive care (BSC) versus oxaliplatin, folinic acid and 5-fluorouracil (OFF) plus BSC in patients for second-line advanced pancreatic cancer: A phase III-study from the German CONKO-study group

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ABSTRACT

Background: Gemcitabine usually given until progressive disease (PD) is the main first-line treatment option for patients with inoperable advanced pancreatic cancer (APC). Currently there is no accepted active regimen for second-line chemotherapy. Previous phase II studies suggest clinical relevant activity of oxaliplatin, folinic acid and 5-FU (OFF). We initiated a phase III multicentre study comparing OFF versus best supportive care (BSC) in patients with APC progressing while on gemcitabine therapy.

Methods: In this open randomized study, patients with CT and/or MRI confirmed progressive disease while on gemcitabine therapy were randomized 1:1 to OFF or BSC. Stratification included duration of first-line therapy (<3, 3 to 6 and >6 months), performance status (KPS 70–80%; 90–100%) and tumour stage (M1/M0). OFF consisted of folinic acid 200 mg/m^2 followed by 5-fluorouracil 2 g/m^2 (24 h) on d1, d8, d15, d22 and oxaliplatin 85 mg/m^2 on days 8 and 22. After a rest of 3 weeks the next cycle was started on d43. A total of 165 patients were calculated to demonstrate a doubling of survival time after progression on first-line therapy.

Results: After inclusion of forty six patients the trial was terminated according to predefined protocol regulations due to insufficient accrual (lack of acceptance of BSC by patients and physicians. Patient characteristics were well balanced between both study arms. The OFF regimen was well tolerated with more patients with grade I/II paraesthesia and grade II/III nausea/emesis and diarrhoea. Median second-line survival was 4.82 [95% Confidence Interval; 4.29–5.35] months for OFF treatment and 2.30 [95% CI; 1.76–2.83] months with BSC alone (0.45 [95% CI: 0.24–0.83], $p = 0.008$). Median overall survival for the sequence GEM-OFF was 9.09 [95% CI: 6.97–11.21] and 7.90 [95% CI: 4.95–10.84] months for GEM-BSC (0.50 [95% CI: 0.27–0.95], $p = 0.031$) respectively.

Interpretation: Although stopped prematurely, this randomized trial provides at first time evidence for the benefit of second-line chemotherapy as compared to BSC alone for

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patients with APC. OFF significantly prolonged survival time compared to BSC alone after failure of first-line therapy with gemcitabine.

1. Introduction

Adenocarcinoma of the pancreas is a highly aggressive cancer, characterized by extensive local invasion, early regional and rapid systemic spread and a high degree of chemo-resistance. In spite of intensive research in the last decade, the 5 years survival rate in patients with advanced pancreatic cancer (APC) is still less than 5%.[1] At present, pancreatic cancer is the fourth most frequent cause of death from solid tumours in the western world.[2] In parallel with disease progression, patients with APC suffer from several symptoms such as abdominal pain, taste abnormalities, nausea and emesis, leading to inadequate nutrition intake, weight loss and fatigue. These symptoms contribute substantially to the deterioration in performance status and quality of life. Gemcitabine (GEM), the standard first-line chemotherapy for pancreatic cancer during the last decade, can lead to improvements of tumour-related symptoms and has shown modest survival advantage.[3] Many multi-agent therapies have been tested but most of them failed to prove superiority over single-agent gemcitabine.[4–6] At the time this trial was planned, best supportive care (BSC) was standard care for patients who progressed on first-line chemotherapy. However, patients with good performance status despite disease progression on gemcitabine therapy generally ask for further anti-cancer therapies. Indeed, several phase-II studies suggested second-line anticancer activity but there are no phase-III studies confirming the benefit of further chemotherapies after progression while on gemcitabine. [7–9] First-line therapy studies report the use of second-line chemotherapies in nearly 30% of patients.[5,6] This clearly underlines the clinical need for evidence based recommendations for patients progressing while on first-line therapy. Based on our phase-II results with the second-line regimen of oxaliplatin, 5-fluorouracil (24 h) and folinic acid (OFF),[10] we initiated the CONKO-003 (CharitéONKOlogie) randomized phase-III trial aimed to investigate the role of OFF + BSC versus BSC alone in patients with APC following disease progression during gemcitabine treatment.

2. Patients and methods

2.1. Eligibility criteria

Patients with histologically confirmed APC who had progressed during first-line gemcitabine therapy were eligible for this open randomized multicentre study. Other major inclusion criteria were: age $\geqslant$18 years; Karnofsky performance status (KPS) > 60%; measurable reference lesion, adequate laboratory values for haematology (white blood cell [WBC] count $>3.5 \times 10^9$/L, platelet count $>100 \times 10^9$/L), renal (creatinine clearance >30 ml/min) and hepatic function (aspartate aminotransferase [AST] or alanine aminotransferase [ALT] < 2.5 × upper normal limit [UNL]; in case of liver metastasis <5 × UNL). Patients were excluded from the study if they had any severe concurrent medical condition interfering with the planned therapy, serious cardiac disease (e.g.: myocardial infarction within the last 4 weeks, unstable coronary heart disease), sensory/motor neuropathy >grade 2, uncontrolled pain, or had previous or active malignancies of other origin. Pregnant or breastfeeding women were excluded. Prior radiotherapy with or without chemosensitization was not allowed. Patients who developed recurrence while receiving adjuvant gemcitabine post curative surgery were not recruited. All patients provided written informed consent. The trial was approved by the Scientific and Research Ethics Committee of the participating institutions. The United States National Health Institute registry number is NCT00786058.

2.2. Treatment

Patients were stratified according to duration of first-line therapy (<3, 3 to <6 and >6 months), KPS (70–80%; 90–100%) and stage (M0/M1) and were randomized to either OFF + BSC or BSC alone. The OFF regimen consisted of a 6 weeks cycle of folinic acid (FA) (0.2 g/m^2, 0.5h, iv.) followed by 5-FU (2 g/m^2,

Table 1 – Patient characteristics.

Treatment	Oxaliplatin, folinic acid and 5-fluorouracil (OFF)	BSC alone
Total number of patients	23	23
Sex		
Male	14 pts	15 pts
Female	9 pts	8 pts
Age		
Median (range)/years	60 [38–76]	61 [34–80]
Median Karnofsky performance status/%	80 (70–100)	80 (70–100)
Stratification		
KPS 70–80%	12 pts	11 pts
KPS 90–100%	11 pts	12 pts
PFS GEM <3 months	6 pts	5 pts
PFS GEM 3–6 months	10 pts	11 pts
PFS GEM >6 months	7 pts	7 pts
M0	6 pts	7 pts
M1	17 pts	16 pts
Pts. with gemcitabine first line therapy	23 pts	23 pts
Progression free survival in 1st line therapy median (months)	4.75	4.57

24-h, iv.) administered on days 1, 8, 15 and 22. Oxaliplatin (0.85 g/m^2, 2–4 h, iv.) was administered prior to FA/5-FU on days 8 and 22. Patients received antiemetic prophylaxis with alizapride and dexamethasone. After a 3 weeks rest (d23 to 42) the next cycle was started (d43 = d1 of next cycle). BSC was provided to all patients according to current palliative care guidelines. BSC included in particular adequate pain management, therapy of infection, biliary-stent intervention if needed, social supply and on demand psychooncologically intervention and nutrition consultation/intervention. Patients in the BSC arm regularly were seen in the outpatient department at least every 14 d. They were visited not so often like patients in the treatment group, but if needed the visit number was equal or even higher. Both groups do not receive additional specific anticancer therapy.

2.3. *Response and toxicity assessments*

Pre-treatment evaluation included a complete medical history and physical examination, blood cell count, standard biochemical profile and a computed tomography scan (CT) or magnet resonance tomography (MRT) confirming disease progression while on gemcitabine. Prior to each treatment cycle a medical history was taken and a physical examination performed. During treatment complete blood cell counts were carried out weekly. Biochemical tests were done at least prior to each cycle and more often in cases of toxicities. A CT- or MRT-scan took place when clinical or laboratory signs suggestive of cancer progression became evident or at least every two treatment cycles.

2.4. *Statistical methods*

The primary study end-point was survival measured from treatment randomization until death or last contact. Secondary end-points were overall survival (OS) from the start of first-line gemcitabine and treatment toxicity.

The sample size calculation was based on the null hypothesis that median patient survival would be 2 months from first-line treatment failure to death ($\mu 1$). The alternative hypothesis was that second-line treatment would lead to an OS of at least 4 months ($\mu 2$) after randomization.

According to these assumptions ($\mu 2$–$\mu 1$, difference $\delta = 2$ months, standard deviation $\sigma = 15$, two-sided test, level of significance $\alpha = 5\%$, power 90%) 165 patients were calculated for the trial, including a drop-out rate of 10%. Data were analysed by SPSS version 13.0 on an intent to treat basis. The probability of survival was estimated by the method of Kaplan

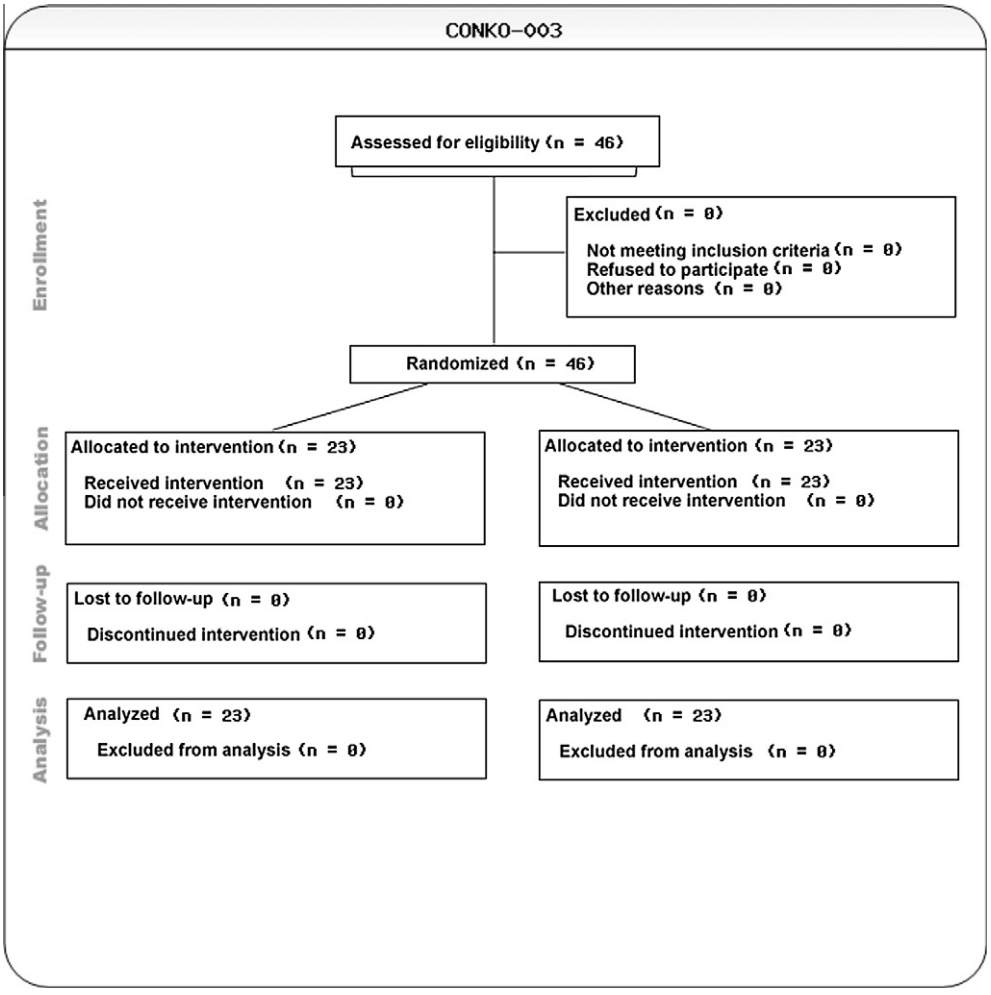

Fig. 1 – Consort diagram.

and Meier, the comparison between the two arms was done using the log-rank test.

3. Results

Recruitment started in December 2002. It was stopped in December 2003 by the protocol committee according to predefined protocol regulations (low recruitment). At that time 46 (OFF + BSC 23 pts/BSC 23 pts) patients from 12 study centres (average pt. recruitment 3) had been included. The major reason for low accrual was due to the diminishing acceptance of BSC alone by oncologists and patients after publishing the phase-II results of the OFF-regimen. Patient characteristics are well balanced between both groups (Table 1, Fig. 1). Patients had been treated with gemcitabine in first-line therapy until progression for a median of 4.57 months (BSC) and 4.75 months (OFF) (HR 0.88 [95% Confidence Interval: 0.49–1.59]; $p = 0.67$).

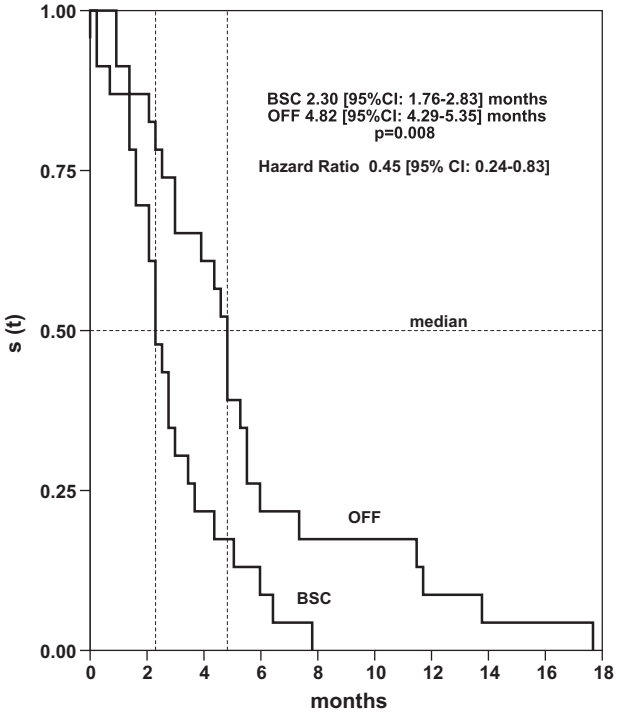

Fig. 2 – Kaplan–Meier plot – second-line survival.

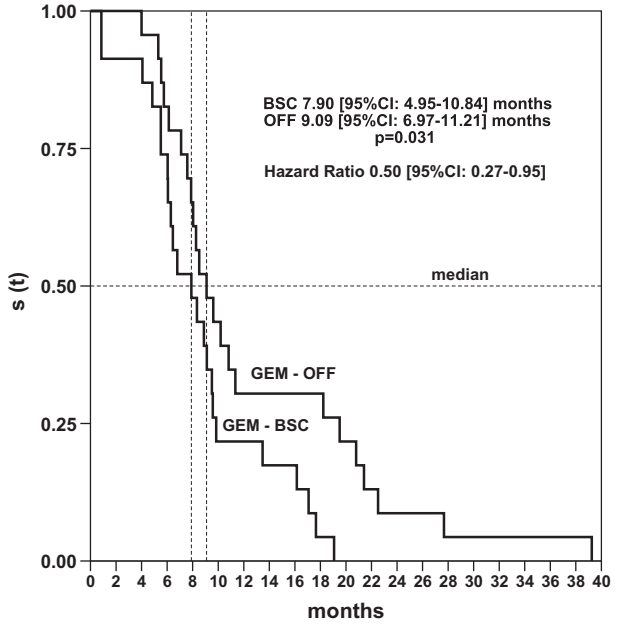

Fig. 3 – Kaplan–Meier plot – overall survival.

Table 2 – Toxicities (NCI-CTC 2.0).

	No. of pts. with toxicity							
	OFF				BSC alone			
	I	II	III	IV	I	II	III	IV
Haemoglobin	5	11	0	0	5	2	1	0
Leucopenia	4	0	0	0	0	0	0	0
Thrombocytopenia	2	2	0	0	0	0	1	0
Diarrhoea	5	1	2	0	1	1	0	0
Nausea/emesis	6	4	1	0	1	1	0	0
Paraesthesia	10	1	0	0	1	0	1	0

3.1. *Efficacy*

Despite the low enrolment numbers, second-line chemotherapy significantly prolonged the survival after first-line progression (Fig. 2). OFF treatment resulted in a median survival of 4.82 [95% CI: 4.29–5.35] months whereas patients in the BSC arm survived for 2.30 [95% CI: 1.76–2.83] months (HR 0.45 [95% CI: 0.24–0.83], $p = 0.008$). No confirmed response better than stable disease was observed. Overall survival was significantly longer in the GEM-OFF sequence with 9.09 [95% CI: 6.97–11.21] months as compared to the GEM–BSC alone sequence with 7.90 [95% CI: 4.95–10.84] months (HR 0.50 [95% CI: 0.27–0.95], $p = 0.031$) (Fig. 3).

The mean administered cumulative dose for oxaliplatin was 281 [0–850] mg for folinic acid 1591 [200–8000] mg and for 5-FU 15630 [2000–20000] mg.

3.2. *Safety*

Side-effects in both groups were given as worst toxicity of all causalities per patient. Moderate haematologic toxicities (NCI-CTC grade 1–2) were reported in 24 patients of the OFF group and in 7 of the BSC group. No grade 3 or 4 haematologic toxicities were reported in the OFF treatment group, one patient in the BSC group experienced a grade 3 thrombocytopenia with non-fatal gastrointestinal bleeding and consequent anaemia grade 3. The most common non-haematologic toxicities were sensory neuropathy, diarrhoea and nausea/emesis. There were no reports of grade 4 non-haematologic toxicities. NCI-CTC grade 1–2 reversible neurotoxicity was seen in 11 (48%) patients in the OFF treatment group. Sensory neurotoxicity was also reported in the BSC group with one pt grade 1 and one pt grade 3 (most likely of paraneoplasic origin) (Table 2).

4. Discussion

Adenocarcinoma of the pancreas remains a malignancy with dismal prognosis. In addition to intensive ongoing research for more effective first-line protocols there is still an unmet

need for evidence-based treatment options other than best supportive care for patients progressing while on gemcitabine therapy. Study results on second-line treatment in this disease are rare. We focused our attention on the combination of oxaliplatin, folinic acid and 5 fluorouracil (OFF) and demonstrated a median overall survival time of 5.05 [0.92–74.82+] months in a phase II study.[10] Another small trial reported a similar survival time (median 5.74 months) but more severe toxicities with these drugs using increased dose intensities,[11] with 57% of the patients requiring granulocyte colony stimulating factor support. Other treatments options had been tested for patients progressing on gemcitabine first-line therapy, too. A combination study of irinotecan and docetaxel was considered too toxic and was therefore stopped prematurely.[12] Weekly docetaxel monotherapy resulted in acceptable toxicity and an overall second-line survival of 3.67 months in 10 patients.[13] Single agent ralitrexed resulted in a remarkable median overall survival of 4.59 months,[14] and for the combination of ralitrexed plus oxaliplatin a similar median survival of 4.82 months and tolerable side-effects were reported.[15] Paclitaxel showed a moderate median survival time of 4.02 months.[8] S-1 resulted in a survival of 4.13 months in 40 patients with acceptable side-effects.[16] Arsenic trioxide in a 13-patient cohort resulted in a survival of 3.44 months.[17] More recently, regimens using combinations of cytotoxic drugs and targeted therapies were investigated in patients after progression during gemcitabine containing first-line therapy. Whereas capecitabine plus erlotinib showed a promising median overall survival of 5.97 months,[9] for the combination of docetaxel plus gefitinib a median survival of 2.52 months was reported.[18]

Second-line treatment options with documented survival times of at least 4–5 months are reported so far only in small phase-II studies. We are not aware of any completed second-line phase-III study in this indication when we initiated our randomized trial of OFF + BSC versus BSC alone.[10] Due to declining acceptance of BSC alone by patients as well as participating oncologists recruitment progressively decreased below 3 pts per months (initial calculation was 3 pts per week) and the study had to be stopped pre term according to protocol.

Both patient groups, although being small, are well balanced with regard to baseline characteristics. The duration of time to progression in first-line treatment with gemcitabine was similar to results of large phase-III first-line trials, ranging from 2.0 to 5.1 months.[19]

Treatment was well tolerated. No grade 4 toxicities were observed. No patient stopped chemotherapy due to side-effects. Despite the small patient cohort we demonstrated a statistically, and clinically as well, significant survival advantage for the chemotherapy cohort, with more than doubling of the median overall survival.

In conclusion, the OFF-regimen represents a feasible and effective approach with acceptable toxicity for second-line outpatient treatment of advanced adenocarcinoma of the pancreas after progression on first-line gemcitabine.

Contributors

UP, IS, JSt, MA, JS, HR and HO contributed to patient enrolment, to the collection and assembly of the data. HR, HO and BD provided capacities for the trial. UP and HR drafted the article. HO, HR and UP were responsible for the study idea, study design, data analysis and interpretation. All authors provided final approval.

Previous presentation of preliminary data

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Conflict of interest statement

None declared.

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