Cancer Chemother Pharmacol (2006) 58: 504–508
DOI 10.1007/s00280-006-0200-2

ORIGINAL ARTICLE

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Adjuvant intra-arterial 5-fluoruracil, leucovorin, epirubicin and carboplatin with or without systemic gemcitabine after curative resection for pancreatic adenocarcinoma

Received: 7 November 2005 / Accepted: 24 January 2006 / Published online: 22 April 2006

Abstract *Background:* The role of adjuvant therapy in pancreatic cancer remains controversial. Gemcitabine given systemically seems to be effective; intra-arterial chemotherapy (IAC) has a deep rationale. *Patients and methods:* The goal was to evaluate the impact of post-operative IAC followed or not by systemic gemcitabine in patients after curative resection for pancreatic adenocarcinoma. 5-fluoruracil 750 mg sqm^{-1}, leucovorin 75 mg sqm^{-1}, epirubicin 45 mg sqm^{-1}, carboplatin 225 mg sqm^{-1} were administered every 3 weeks into celiac axis for three cycles (FLEC regimen), then gemcitabine at the dosage of 1 g sqm^{-1} on days 1, 8 and 15 every 4 weeks for 3 months (FLECG regimen). *Results:* Forty-seven patients entered the study. The first 24 received only IAC (FLEC regimen), the other 23 received the same intra-arterial regimen followed by systemic gemcitabine (FLECG regimen). After a median follow-up of 16.9 months, 29 patients recurred (61.7%). Median disease free survival (DFS) was 18 months and median overall survival (OS) was 29.7 months. One-year DFS was 59.4% and 1-year OS was 75.5%. Main grade 3 toxicity related to IAC was only nausea/vomiting in 4%; regarding gemcitabine, grade 3 toxicities were anaemia 8%, leukopenia 8%, thrombocitopenia 17%, nausea/vomiting 4%. *Conclusions:* FLEC regimen with or without gemcitabine is active with a very mild toxicity and results are very encouraging in an adjuvant setting.

Keywords Adjuvant chemotherapy · Gemcitabine · Intra-arterial chemotherapy · Pancreatic cancer

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Introduction

Surgery offers the only chance of cure for pancreatic adenocarcinoma but only 10–15% of patients are suitable for resection due to the presence of locally advanced or metastatic disease: the majority of patients submitted to surgery relapses both locally and at distance with median survival of 13–18 months and with 5-year survival at best of 15–20% [1, 2]. More radical pancreatic resections and extended lymphadenectomy have failed to produce significant survival advantage [3]. In the United States, adjuvant treatment with fluoruracil-based chemoradiation is frequently recommended even if these data have been translated from a study of 43 patients enrolled over 9 years [4]. In Europe a recent randomised, widely criticised trial concluded that standard care for patients with resectable pancreatic cancer should consist of curative surgery followed by adjuvant systemic chemotherapy [5]. Adjuvant gemcitabine seems to improve

disease free survival (DFS) and even if data are not yet mature, survival curves have separated [6]. One way of research is oriented to find new integrated strategies and new routes of administration able to deliver drug dose to the tumour in order to overcome the drug resistance. Regional chemotherapy attempts to maximise the dose of cytotoxic agent reducing systemic side effects. Intra-arterial chemotherapy (IAC) has been evaluated in advanced pancreatic cancer and preliminary results have demonstrated interesting response rates and survival in some series [7, 8].

Based on our previous trial about IAC in locally advanced and metastatic pancreatic carcinoma [9], and on the encouraging results of some adjuvant intra-arterial phase II trials [10–12], a study of FLEC regimen infused into celiac axis followed or not by systemic gemcitabine in patients submitted to curative surgery for pancreatic adenocarcinoma was started in January 1998.

In this trial we have used drugs with proven efficacy in pancreatic cancer at conventional dose without hemofiltration and with a pharmacologic advantage in terms of concentration when administered arterially [9].

Patients and methods

Patient population

Patients submitted to curative surgery for pancreatic adenocarcinoma entered into the study. Eligibility criteria were Karnofsky performance status > 70, white blood cell count > 3,000 mm^{-3}, platelet count > 120,000 mm^{-3}, haemoglobin level > 10 g dl^{-1}; total bilirubin and serum creatinine level were required to be < 1.5 times the institutional upper limit of normal. Patients were excluded from the study if they had any of the following: concomitant second malignancy, with the exception of treated basal cell carcinoma of the skin or cured cervical cancer; concurrent treatment with other experimental drugs; another serious illness or medical condition. All patients gave their informed consent according to our institutional guidelines and the study has been carried out with ethical committee approval.

Study design

Three cycles of chemotherapy were administered every 3 weeks through an angiographic catheter (Simmons 2; 5 Fr) introduced via the femoral artery into celiac axis. Each drug was diluted in 100 ml of normal saline and then infused by bolus one after the other in the following order: folinic acid 75 mg sqm^{-1}; 5-fluoruracil 750 mg sqm^{-1}; epirubicin 45 mg sqm^{-1}; carboplatin 225 mg sqm^{-1}. Supportive antiemetic (granisetron 8 mg) and anti-H2 blocker (famotidine 40 mg) were given intravenously (FLEC regimen). Since June 2002 after three cycles of locoregional therapy, gemcitabine was infused systemically at the dosage of 1,000 mg sqm^{-1} weekly for 3 weeks every 4, over 3 months (FLECG regimen). Pretreatment evaluation included medical history, a physical examination, complete blood cell count, biochemical profile, Ca 19-9 value, ECG, and abdominal CT scan. Blood cell count was evaluated on days 10, 14 and 18 after IAC. Before each subsequent cycle patients underwent a physical examination, complete blood cell count, and biochemical profile. CT scan and Ca 19-9 were repeated at the end of IAC and after systemic gemcitabine, then every 3 months or when there was a suspicion of recurrence. Toxicity was graded by the National Cancer Institute Common Toxicity Criteria version 2.0 [13].

Statistical analysis

The aim of this prospective trial was the assessment of feasibility of FLEC regimen given intra-arterially in adjuvant setting with or without the sequential addition of systemic gemcitabine (FLECG regimen).

The primary end point of the study was 1-year DFS. The target enrolment was estimated to be 46 patients, according to the Simon Two Stage Optimal Design [14] with the lower proportion of interest of 40% and the target proportion of interest of 60% ($\alpha = 0.05$ and $\beta = 0.20$).

The strategy would be considered to deserve further analysis if at least 23 patients were disease free at 1 year. DFS was defined as the interval between surgery and the first evidence of recurrent disease or death whichever occurred first. Overall survival (OS) was considered from surgery to death or to the last follow-up assessment and survival time was calculated using the Kaplan–Meier method. Univariate analysis was used to calculate survival probabilities in relation to clinical variables (gender, age), tumour related variables (size, site, grading, nodal status, Ca 19-9 level) and treatment related variables (lymph nodes dissection, resection margins, adjuvant treatment): survival curves were estimated with the Kaplan–Meier method and compared by use of the log-rank test.

Results

Since January 1998, 47 patients from four surgical departments (two in Verona, Mantova, Carrara) were enrolled onto the study. Patients' characteristics are listed in Table 1. The first group (January 1998–May 2002) included 24 patients that received only three cycles of FLEC regimen, the second group (June 2002–December 2004) included 23 patients that received also systemic gemcitabine after three cycles of intra-arterial chemotherapy (FLECG regimen). The median time from surgery to chemotherapy was 45.5 days (range 29–84). A total of 137 intra-arterial cycles and

Table 1 Patients'characteristics

Regimen	FLEC	FLEC-G
Number	24	23
Age (years)		
Median	60	62
Range	28–78	33–74
Sex		
Male	14	14
Female	10	9
Karnofsky PS		
90–100	11	11
70–80	13	12
Tumour site		
Head	19	20
Body	3	3
Tail	2	
Tumour size (cm)		
Median	3.0 (1.2–5)	2.5 (0.5–5)
Histology		
Adenocarcinoma	23	23
Acinar cell adenocarcinoma	1	0
Tumour grade		
1	1	1
2	13	14
3	10	8
Stage		
II ($T_3N_0M_0$)	7	2
III (T_1–$T_3N_1M_0$)	14	21
Iva ($T_4N_{any}M_0$)	3	0
Lymphoadenectomy		
Extended	9	7
Standard	15	16
Number of lymph nodes		
Median	15.0	21.0
Range	4–53	5–60
Lymph node		
N0	7	2
N1	17	21
Resection margins		
R0	15	19
R1	9	4

198 weekly gemcitabine cycles were administered. All the patients except two completed the IAC scheduled program: one did not because early progression of disease and one because refusal. Nine cycles of gemcitabine were not administered because of thombocytopenia in four patients.

Disease free survival and overall survival

Twenty-seven patients (57.4%) were disease free at 1 year from surgery. Median DFS and OS for the whole series were 18 and 29.7 months, respectively.

In FLEC group, after a median follow-up of 27 months (4.1–65), 18 out of 24 (75%) relapsed and the sites of the first recurrences were, respectively, local in six patients, peritoneal in six, hepatic in six and extra-abdominal in two. Median DFS was 14 months with 1- and 2-year DFS of 54 and 38%, respectively. Median survival was 24.8 months with 1- and 2-year OS of 67 and 58.3%, respectively.

In FLECG group, after a median follow-up of 14 months (4–39), 11 out 23 (48%) relapsed and the sites of the first recurrences were, respectively, local in six patients, peritoneal in five, hepatic in four and extra-abdominal in one patient. Median DFS was 22 months with 1- and 2-year DFS of 65 and 47%, respectively. Median survival was not reached and 1- and 2-year OS were, respectively, of 88 and 70%.

Toxicity

No side effects related to angiographic technique were observed. Table 2 shows systemic toxicity related to the IAC (all 47 patients are evaluable) and to gemcitabine (all 23 patients are evaluable). IAC was well tolerated, with only 4% of grade 3 nausea/vomiting and no other grade 3/4 toxicity. About systemic treatment, we observed a grade 3 anaemia in 8%, a grade 3 leukopenia in 8%, a grade 3 thrombocytopenia in 17% and a grade 3 nausea/vomiting in 4% of patients.

Discussion

Adjuvant treatment's aim is to improve survival by treating subclinical residual tumour. There is no globally accepted standard for adjuvant therapy in pancreatic cancer and the use of chemotherapy has a strong rationale, principally because radiotherapy only decreases loco-regional recurrence without any changes in hepatic, peritoneal and systemic progression [15, 16].

Preliminary results of the first adjuvant randomised trial of gemcitabine are very encouraging showing a DFS almost twice as long for the treated patients, 14.2 months for the gemcitabine group compared with 7.5 months for the observation group ($P < 0.001$). This advantage remains regardless of whether margins were positive or negative or whether nodes were involved. At the time of presentation OS data were not yet mature, but the curves had separated [6]. The main aim of regional chemotherapy is delivery of high doses of chemotherapic agents to the principal focus of recurrent disease, liver and pancreatic bed and yet minimise systemic toxicity. Celiac axis, portal vein and hepatic artery have been used to administer different chemotherapic agents. Ishikawa et al. [11] placed catheter in hepatic artery and in portal vein and infused 5-fluoruracil continuously over 4–5 weeks after radical surgery in 27 patients. There was a significant improvement in 1- and 3-year survival: 62 and 35% for historical control versus 92 and 51% for the treated group, with an impressive decrease of hepatic recurrence. The group of Papachristou treated 31 patients with six cycles of mitoxantrone, 5-fluoruracil, folinic acid and cisplatin infused via celiac axis in 5 days every 5 weeks and achieved a median survival of 21 months with a liver recurrence rate of 15% [12]. With regard to treatment sequence

Table 2 Toxicity profile

	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)
Toxicities of intra-arterial chemotherapy (137 cycles in 47 patients)				
Anaemia	8	17	0	0
Leukopenia	4	2	0	0
Thrombocytopenia	6	0	0	0
Nausea/vomiting	6	6	4	0
Diarrhoea	4	0	0	0
Alopecia	0	8	0	0
Toxicities of systemic chemotherapy (198 weekly administrations in 23 patients)				
Anaemia	17	17	8	0
Leukopenia	17	13	8	0
Thrombocytopenia	13	17	17	0
Nausea/vomiting	8	8	4	0
Diarrhoea	4	4	0	0

(at first IAC and then systemic gemcitabine), it seems more rationale to treat subclinical disease that probably grows into the liver and into pancreatic bed with a higher drug concentration at first pass. The current study showed that FLEC regimen with or without gemcitabine is tolerated without any significant toxicity after radical surgery for pancreatic adenocarcinoma. Primary end point of the trial, that was to maintain at least 23 of 47 patients free of disease at 1 year from surgery, was completely obtained with 27 patients (57.4%) without any recurrence of disease after 1 year.

Regarding OS, when we consider all the patients, we observed a median of 29.7 months with a 1- and 2-year survival of 75 and 60%, respectively. It was not possible to make a statistical comparison between the two groups because the sample size is inadequate and the FLECG group follow-up is shorter than FLEC one with a limited number of events. However 1-year OSs are 67 and 88% for FLEC and FLECG, respectively (Fig. 1).

This result reflects what happens in advanced pancreatic cancer where PEFG regimen has shown a more favourable outcome in terms of progression free survival and OS than gemcitabine alone [17]. Also our study includes an antifolate, an anthracicline, a platinum compound and gemcitabine, all active drugs in pancreatic cancer.

Negative prognostic factors result only in undifferentiated tumour (G3) and nodal involvement (>3 nodes): these data confirm the relevance of the biological behaviour of the tumour in our study.

Toxicity after intra-arterial administration is mild with a very good compliance: side effects related to the technique and grade 4 toxicity were not observed: grade 3 nausea/vomiting was seen in 4% of the patients. The absence of haematological grade 3–4 toxicity compared with FLEC regimen used in patients with locally advanced and metastatic pancreatic adenocarcinoma [9] is due to the dose reduction of 25% that we applied in adjuvant setting.

Liver metastases have been reported to occur in up to 90% of patients after pancreatic surgery [1]. IAC seems to reduce the rate of hepatic recurrence also in this trial, where we observed 10 out of 47 patients (21%) with liver recurrence as first site of relapse. This is probably related to the high drug concentration reached in the liver during the first pass of the drug administered intra-arterially.

In our series it is not possible to compare the two different patterns of failure regarding the addition of systemic gemcitabine (FLEC and FLECG) because the small number of patients and the different median follow-up. However, it seems that FLECG might have a better impact on all kinds of recurrence except local one.

Even if to compare with other adjuvant studies is not appropriate, the median OS obtained with our regimen is very encouraging and suggests further evaluations.

In conclusion, many paradigms about the treatment of pancreatic cancer have been changing this year. In advanced disease the combination of gemcitabine plus the oral EGFR (epidermal growth factor receptor) tyrosine kinase inhibitor erlotinib was compared with gemcitabine plus placebo and has shown a statistical improvement in survival [18]. This is the first evidence of the benefits of EGFR tyrosine kinase inhibitors in combination with chemotherapy. Similar trials assessing bevacizumab and cetuximab are ongoing. A four-drug regimen (PEFG) was associated with improvements in both tumour response rate and progression free survival

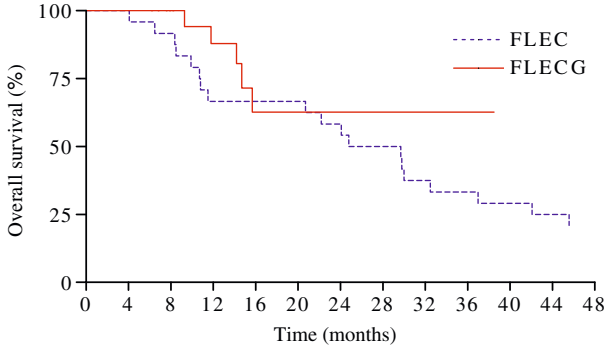

Fig. 1 Overall survival of patients treated with FLEC (24) and FLECG (23) regimen

when compared with gemcitabine alone with a small but significant improvement in OS [17]. In adjuvant setting gemcitabine compared to surgery alone significantly increases DFS [6]. This is the first evidence of a substantial benefit from chemotherapy in resected patients. Our study, with its limits of a small sample size (47 patients), a long time of enrolment (7 years), a not widely accepted locoregional technique (celiac axis bolus infusion), is in the direction of a four-drug regimen in the treatment of pancreatic cancer: it appears feasible without significant toxicities and results in terms of DFS and OS should not be ignored.

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