Intra-arterial Infusion of 5-Fluorouracil, Leucovorin, Epirubicin and Carboplatin (FLEC regimen) in Unresectable Pancreatic Cancer: Results of a Ten-year Experience

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Abstract. The final results of a new regimen given intra-arterially for unresectable pancreatic cancer (UPC) are presented. Patients and Methods: From January 1994 to January 2006, 5-fluorouracil 1,000 mg/m², leucovorin 100 mg/m², epirubicin 60 mg/m² and carboplatin 300 mg/m² were administered every 3 weeks into the celiac axis (CA) angiographically (FLEC regimen) to 211 patients with UPC. Results: Seven hundred and sixty-four cycles were administered. Grade 3-4 hematological toxicity was observed in 24%; ematemesis in 4%; grade 3 gastrointestinal toxicity in 3%; grade 3 alopecia in 15%. One sudden death, a pre-infarction angina and a transitory ischemic attack were observed. No complications related to the angiographic procedure took place, but three tunica intima dissections of the iliac artery occurred; 7.6% of patients with partial responses and 50.7% with stable disease were observed. Two hundred and one patients have died; median overall survival was 9.2 months: 10.5 and 6.6 for stage III and IV, respectively. Conclusion: The FLEC regimen given intra-arterially is well-tolerated and effective in patients with UPC.

Carcinoma of the exocrine pancreas is the fifth leading cause of death from malignant disease in Western countries. The diagnosis is generally late and only 10-20% of the patients are in stage I or II at the time of diagnosis. Ninety-nine percent of patients with pancreatic adenocarcinoma die of their disease, with an overall 5-year survival rate of less than 4% (1). Late diagnosis, chemoresistance and radioresistance of pancreatic cancer are the main reasons for the poor therapeutic results (2).

Currently, standard treatment for patients with unresectable pancreatic adenocarcinoma is systemic gemcitabine (GEM), with only a small, but significant advantage in terms of survival and clinical benefit, if compared with best supportive care (3). Up to now, no combination of GEM with another chemotherapeutic agent has been shown to be clearly superior to GEM alone. Recently, a four-drug regimen (gemcitabine, cisplatin, epirubicin and 5-fluorouracil; FLEC regimen) has been associated with improvement in both tumor response rate and progression-free survival when compared with gemcitabine alone, with a small, but significant improvement in overall survival (OS) (4). A number of ongoing trials are exploring the potential benefit of GEM with novel agents, such as antibodies to the epidermal growth factor receptor and vascular endothelial growth factor. In 2005, a randomized phase II study comparing GEM alone versus GEM plus erlotinib (an oral epidermal growth factor receptor tyrosine kinase inhibitor) had shown a statistical improvement in survival for the combination treatment (5). Intra-arterial chemotherapy for the treatment of pancreatic cancer has been evaluated and preliminary results have indicated that pancreatic cancer is dose dependently sensitive to regional chemotherapy and that the method offered interesting response rates, survival and quality of life in some uncontrolled small trials (6-11). This year, the FLEC regimen with or without systemic GEM as...
adjuvant treatment after curative surgery, has demonstrated good tolerance and promising results in term of disease-free survival and overall survival (12). The present multicentric study has been performed to determine the feasibility, the toxicity and the real impact of a new and very simple loco-regional approach in the treatment of unresectable pancreatic cancer (UPC).

**Patients and Methods**

**Eligibility criteria.** From January 1994 to January 2006, 211 patients with exocrine pancreatic cancer entered the study, approved by our ethical review committee. Patients were required to have biopsy-proven adenocarcinoma of the pancreas, not suitable for curative resection. The other inclusion criteria were: Eastern Cooperative Oncology Group (ECOG) performance status less than 3, pre-treatment WBC count >3,000/µl, platelet count >120,000/µl and hemoglobin level >9.5 gm/dl, total bilirubin and serum creatinine levels <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 or another serious illness or medical condition. All patients gave their informed consent according to our institutional guidelines. Staging included total abdomen CT-scan, chest X-ray and Carbohydrate-antigen (Ca 19-9). Weight, pain intensity and analgesic consumption, performance status and Ca 19-9 were evaluated at the time of study entry and after each cycle.

**Treatment.** Three cycles of chemotherapy were administered every 3 weeks through an angiographic catheter (Simmons 2; 5 Fr) introduced via the femoral artery into the celiac axis (CA). Each drug was diluted in 100 ml of normal saline and then infused by bolus one after the other in the following order: leucovorin 100 mg/m², 5-fluorouracil 1,000 mg/m², epirubicin 60 mg/m², carboplatin 300 mg/m² (FLEC regimen). Supportive antiemetic (granisetron 8 mg) and anti-H2 blocker (famotidine 40 mg) were given intravenously. Every cycle required two days of hospitalization. Hematological growth factor (filgrastim) was given at a dose of 5 µg/kg/d from day 8 to day 12. The response was evaluated after three cycles; in the case of a clinical response, independently from CT-scan response, another three cycles were administered. The primary end-point of the study was the evaluation of the effect of loco-regional intra-arterial chemotherapy on the disease related symptoms (pain and weight loss) and on measurable disease. The secondary end-point was the evaluation of the progression-free survival and overall survival.

**Response.** All patients were evaluated for response on the basis of the intention to treat.

1. **Clinical response.** Pain: Before each cycle, subjective pain intensity was evaluated by a Visual Analogic Scale (VAS), from 0 to 100 millimetres. An improvement of at least 50% in respect to baseline level for 4 weeks or more, was considered to be a positive response. The objective pain intensity was also evaluated by analgesic consumption: grade 1=no therapy required; grade 2=only non-steroidal anti-inflammatory drugs (NSAIDs); grade 3=a combination of NSAIDs, antidepressants and anticonvulsants; grade 4=morphine derivatives (MD); grade 5=a combination of MD, NSAIDs, antidepressants and anticonvulsants. It was considered that pain-CR was achieved when grade 1 was reached for 4 weeks or more; pain-PR when there was a decrease by two or more grades; pain-SM when there was a decrease by one grade or no changes appeared; pain-PD when there was an up-staging by one or more grades.

2. **Weight:** Weight was evaluated just before the first treatment and before each successive cycle: a weight gain of >7% from baseline, sustained for >4 weeks was considered as a positive response.

3. **Objective response.** CT-scan: The antitumor efficacy of the treatment was observed by CT-scan according to the standard SWOG response criteria(13).

4. Ca 19-9: A CR was recorded when the value entered into the normal range, a PR when there was a decrease of more than 50% of the initial value, a PD for any increase and a SD when there were none of the previous criteria.

After the end of therapy, patients were evaluated every three weeks by oral and physical examination, complete blood counts, chemistry profiles and urine analyses. All signs, symptoms or laboratory abnormalities were assessed using WHO criteria for toxicities.

**Statistical analysis.** Statistical analysis was performed using the statistical package SPSS for Windows version 13.0. In addition to the objective (radiological and hematological) responses and to the clinical response, the progression-free survival and the overall survival, calculated as the interval between the start of therapy and the last follow-up or death were also assessed, using the Kaplan-Meier method.

**Results**

**Patient population.** Two-hundred and eleven patients were entered into this study from five different institutions. Patient characteristics are listed in Table I. At the baseline (before treatment), pain was present in 182 patients (86.2%) and the median VAS value was 40 millimetres. Regarding analgesic consumption, seventy patients had scored grade 2, sixty-three grade 3, forty-one grade 4 and eight grade 5.

**Treatment summary.** A total of 764 treatment cycles were administered with a mean of 4.0 for stage III patients (range 1-6) and 3.3 for stage IV patients (range 1-6). All patients were evaluated for response and survival on the basis of the intention to treat.

**Toxicity.** All 211 patients were assessed for toxicity. Twenty-four per cent of them had grade 3-4 hematological toxicity. A grade 3-4 anemia was observed in 9%; a grade 3-4 thrombocopenia in 24.1% with a median platelet nadir of 75,000/µl on day 14 and a grade 3-4 leukopenia in 12.8% of the patients with a median leukocyte nadir of 1,200/µl on day 16. Four cases of ematemesis with a debilitating blood loss were observed during the thrombocytopenic period. Non-hematological toxicity was mild: vomiting requiring therapy in 3.3% of the patients, grade 3 diarrhea in two patients and severe abdominal pain in four patients.
two patients had grade 3 alopecia (15.1%). There was a sudden death on day 23 after the third cycle: the patient had well-compensated ischemic cardiopathy and had had a diaphragmatic myocardial infarction four years before treatment; a pre-infarction angina appeared in a patient after the second cycle; a transitory ischemic attack in a patient on day 2 after the first cycle; in only three patients it was not possible to complete the treatment because of intimal dissection of the iliac artery.

Response and survival. Response data are listed in Table II.

**i) Clinical response. Pain:** With regard to subjective pain intensity, an improvement of at least 50% in respect of the VAS basal level was seen in 71 patients (39%); regarding analgesic consumption, 67 out of 182 had Pain-CR (36.8%), 10 out of 182 Pain-PR (5.5%), 86 out of 182 Pain-SD (47.3%) and 19 out of 182 Pain-PD (10.4%).

**Weight:** A weight gain of >7% from the baseline was observed in 17 out of 182 had Pain-CR (36.8%), 10 out of 182 Pain-PR (5.5%), 86 out of 182 Pain-SD (47.3%) and 19 out of 182 Pain-PD (10.4%).

**ii) Objective response.** CT-scan overall response rates were 16 PR (7.6%), 107 SD (50.7%) and 19 PD (9%); 69 patients (32.7%) were not assessable because of early deaths or because treatment was stopped before the third cycle.

**Ca 19-9:** A CR in 18 out of 211 (8.5%), a PR in 89 out of 211 (42.2%), a SD in 28 out of 211 (13.3%) a PD in 76 out of 211 (36%).

**iii) Survival:** The median time to clinical progression was 5.5 months. Median overall survival was 9.2 months (10.5 months for stage III and 6.6 months for stage IV).

**Sites of progression.** In 99 stage III patients a peritoneal progression was observed in 52 (52%) and a progression of the primary tumor in 48 (48%). A liver progression was present in 34 (35%); a local progression without liver progression in 58 (58%) and liver progression without local progression in 4 (4%).

**Discussion**

Pancreatic cancer is considered a chemoresistant tumor and up to now an individual drug with a high level of activity has been lacking. The most important reasons for this drug resistance, are the presence of both a biological and a mechanical "barrier". The first is the multidrug resistance
gene (MDR1) product and the second a very dense, poorly vascularized, fibrotic envelope that is almost impenetrable by drugs (14-16).

To improve tumor response different methods of regional administration have been evaluated. One way to increase the drug concentration within the tumor is to perfuse the arterial blood supply directly (17). For pancreatic cancer, this method is anatomically practicable, and is justified by the biological natural history of pancreatic cancer: the pattern of metastatic spread is largely confined to the abdominal organs within the arterial supply of the celiac axis and takes place in a stepwise manner via venous routes, first to the liver, and only 27% of extra-abdominal metastases have been reported (18, 19). The feasibility and the efficacy of intra-arterial chemotherapy for the treatment of pancreatic cancer has been evaluated with several combination regimens and using different methods, such as five-day celiac axis infusion, celiac axis stop flow infusion, abdominal stop flow hypoxic perfusion, regional chemotherapy with hemofiltration and one-day intra-arterial chemotherapy (8-11). All have shown promising response rates with improved median survival times and quality of life. Based on our previous experience with carboplatin, we added carboplatin and epirubicin to the current standard drug, 5-fluorouracil, and modulated it with leucovorin (20-22). Comparison of the feasibility, compliance and the results of our one-day intra-arterial regimen with other more complicated techniques, such as abdominal stop flow perfusion, regional chemotherapy with hemofiltration and 5-day celiac infusion, supported our opinion that it was the simplest, cheapest and most acceptable regional approach. The overall survival was 9.2 months; 10.5 and 6.6 months for stage III and IV, respectively. With the other loco-regional approaches the median survival rates have been reported as: 12 months with abdominal stop flow perfusion or infusion; 7.5 months with five-day celiac axis infusion and 13 months with regional chemotherapy and hemofiltration (7-9). The CT-scan responses with regional therapy have varied from 7.6% in our study to the 69% observed by Aigner et al., while Link et al. have reported a PR of 21% and Muchmore a PR of 45%. These differences indicate that the objective response rates have not always been uniformly determined, but they do not modify the survival rate or the results on quality of life. The effort to identify a reproducible method of evaluating the quality of life by clinical benefit response is a justified approach (23).

In stage III patients the site of progression was evaluated: peritoneum 52%, primary tumor 48%, liver 35%, a local progression without liver metastases in 58% and liver progression without local progression in only 3%. In stage III patients the expected liver progression and also the expected liver progression without local progression could have been higher than the 35% and 3% we have reported. This data seems to suggest a better control on hepatic progression which confirms the results of Ohigashi et al. (24) and Link et al. (25). Most of the patients failed due to progression of uncontrolled peritoneal metastases. Our study has shown that the FLEC regimen given through an intra-arterial infusion was feasible and effective, it required only one day of hospitalization and might become an interesting form of integrated strategy in the treatment of pancreatic cancer.

References


