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# Phase II trial of 5-fluorouracil, Adriamycin and cisplatin (FAP) followed by radiation and 5-fluorouracil in locally advanced pancreatic cancer

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**Summary.** A total of 19 patients (7 men, 12 women) with locally advanced pancreatic adenocarcinoma were treated with six cycles of FAP (5-fluorouracil, 300 mg/m$^2$ i.v. on days 1–5; Adriamycin, 50 mg/m$^2$ i.v. on day 1; cisplatin, 20 mg/m$^2$ i.v. on days 1–5). Each course was repeated every 28 days. After six cycles, the treatment was followed by irradiation amounting to 4,000 cGy (split course) in combination with 5-FU (500 mg/m$^2$) on days 1–3 of the two irradiation periods. The median age of our patients was 55 years (range, 40–64 years). The median WHO performance status was 1, with a range of 0–2. Three (16%) complete (CR) and six (31%) partial responses (PR) were observed, as were six cases of stable disease (SD) and four of progressive disease (PD). The median duration of response was 11 months, with a range of 4–24 months, and the median survival was 14 months (range, 5–27 + months). FAP toxicity was tolerated fairly poorly. The dose-limiting toxic effect was myelosuppression, with a mean WBC nadir of WHO grade 1.6 (range, 0–3) and a mean platelet count of WHO grade 1.1 (range, 0–4). Nausea and vomiting were not dose-limiting. Complete alopecia was seen in 14/19 patients. Neuropathy was mild (WHO grade 1) in seven and moderate (grade 2) in four. Irradiation in combination with 5-FU was generally well tolerated. Due to several reasons, only ten patients could be treated with all six cycles of FAP. We conclude that in future combined modality studies, irradiation should be given after three cycles of chemotherapy, and that combined modality treatment for locally advanced pancreatic cancer is feasible and warrants further testing.

## Introduction

The incidence of adenocarcinoma of the pancreas has steadily increased over the past four decades [14]. Despite tremendous efforts in early diagnosis and therapy, the prognosis is still dismal. The overall survival is 0.4%; the prognosis is poor, even in patients who have undergone surgery. The review of the literature by Gudjonsson [5] reveals that no investigator has obtained a 5-year survival of >3.4%. The high mortality associated with pancreatic cancer is partly due to the low resectability of the tumor at the time of diagnosis: the malignancy is often not detected until either regional extension or distant metastasis has occurred.

Locally advanced cancer of the pancreas defines that stage of unresectable disease in which the tumor involves regional nodes and encases major blood vessels, but without evidence of hepatic or distant metastases. It is possible to encompass the tumor in a moderately sized upper gastrointestinal radiation port. Approximately 40% of patients with pancreatic cancer present with this stage [15]; its presently accepted management involves the use of combined modality treatment with 5-fluorouracil (5-FU) and radiation therapy [7].

The objective of the present study was to define the role of chemotherapy in the form of the FAP regimen [consisting of 5-FU, Adriamycin (ADM), and cisplatin (CDDP)] followed by irradiation given in combination with 5-FU. We have previously reported the activity of FAP in advanced gastric cancer [17].

## Materials and methods

A total of 19 patients (7 men, 12 women) with locally advanced pancreatic cancer were treated with FAP followed by irradiation combined with 5-FU. Before this treatment schedule started, 11 patients had unergone a gastrojejunostomy and/or a choledocho- or cholecysto-jejunostomy; the diagnosis for 17 patients was proven by biopsy and that of 2, by cytology only. The median age of the patients was 55 years (range, 40–64 years) (Table 2). The median WHO performance status was 1, with a range of 0–2. The FAP chemotherapy regimen was given according the following schedule: 5-FU, 300 mg/m$^2$ i.v. on days 1–5, ADM, 50 mg/m$^2$ i.v. on day 1; and CDDP, 20 mg/m$^2$ i.v. on days 1–5. The course was repeated every 28 days. The drug dose was modified for subsequent courses according to the degree of hematological toxicity (Table 1). The dose of ADM was reduced by 50% in the presence of a bilirubin level of 35–50 mmol/l; no ADM was given if this level reached >50% mmol/l.

After six cycles of FAP, the patients were given irradiation therapy as described by the Gastrointestinal Tumor Study Group [7], consisting of 4,000 cGy (split course) in combination with 5-FU (500 mg/m$^2$) on days 1–3 of the two irradiation periods of 2 weeks each, with an interval of

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**Table 1.** Dose attenuation schedule for bone marrow depression

| | Leukocytes ($\times 10^9$/l) | Thrombocytes ($\times 10^9$/l) | 5-FU | ADM | CDDP |
|---|---|---|---|---|---|
| a | >4 | >150 | 100% | 100% | 100% |
| b | 3–4 | 100–150[a] | 75% | 50% | 100% |
| c | 2–3 | 100–150[a] | 50% | 25% | 75% |
| d | <2 | <100 | 0 | 0 | 0 |

[a] The dose was postponed for 1 week and adjusted thereafter. If no recovery to level c or higher was seen after 1 week, the patient underwent irradiation after recovery

2 weeks. The patients were evaluated for response after three cycles of chemotherapy, after the end of chemotherapy, and 6 weeks after the irradiation period. The response was assessed by computerized tomography (CT) and ultrasonography. When the results of these investigations did not agree, the result of the CT scan was used as the standard.

The response was defined according to WHO guidelines for nonmeasurable disease [19]. A complete response (CR) was therefore defined as the complete disappearance of all known disease. A partial response (PR) was defined as an estimated decrease in tumor size of $\geqslant 50\%$, and no change (NC) was defined as no significant change. The latter included stable disease (SD), an estimated decrease in tumor size $<50\%$, and lesions with an estimated size increase of $<25\%$. Disease progression (PD) was defined as the appearance of a new lesion not previously identified or an estimated increase of $\geqslant 25\%$ in the size of existent lesions. The results required a minimum of 4 weeks' observation after the initiation of treatment. The duration of response and of survival were measured from the start of chemotherapy. Toxicity was assessed using a 0–4 grading system according to WHO [20].

## Results

Of the 19 patients, only 9 could be treated exactly according to the protocol (Table 2). All patients, however, received a minimum of three cycles of chemotherapy, after which three patients achieved a clinically complete remission and six a partial regression; ten patients had stable disease. Because of prolonged leucocytopenia, two patients underwent irradiation after three cycles. Two other patients had progressive disease after four cycles, and one, after five cycles. One patient refused further treatment after four cycles. In two patients there was an incorrectly interpreted evaluation of data, leading to suspicion of disease progression after five cycles; these patients therefore received subsequent irradiation. One patient had progressive disease during irradiation, and one patient did not want to take the second part of the irradiation. Evaluation of the patients who finished their radiation therapy revealed no further tumor regression after irradiation. The median time to progression for the whole group was 11 months, with a range of 4–24 months. The median survival for the whole group was 14 months, with a range of 5–27 + months.

### *Toxicity*

The FAP regimen was tolerated fairly poorly, and the dose-limiting toxic effect was myelosuppression. The mean WBC count per cycle was WHO grade 1.6 (range, 0–3); the mean platelet count was WHO grade 1.1 (range, 0–4). All patients were treated with antiemetics. Nausea and vomiting were not dose-limiting. Complete alopecia

**Table 2.** Patient characteristics and response data

| Treatment: | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Patient: | | | | | | Response after: | | duration (months): | |
| Number | Age | Sex | Performance status | Cycles (*n*) | +/− RT | 3 cycles | End of treatment | Response | Survival |
| 1 | 61 | F | 1 | 6 | + | CR | CR | 24 | 27 |
| 2 | 61 | M | 2 | 6 | + | PR | PR | 18 | 18 |
| 3 | 50 | F | 1 | 6 | + | SD | SD | 13 | 17 |
| 4 | 60 | F | 1 | 6 | + | PR | PR | 14 | 17 |
| 5 | 47 | F | 0 | 6 | + | SD | SD | 11 | 17 |
| 6 | 45 | M | 1 | 6 | + | PR | PR | 14 | 16 |
| 7 | 64 | F | 1 | 6 | + | SD | SD | 13 | 15 |
| 8 | 62 | F | 1 | 6 | + | SD | SD | 14 | 14 |
| 9 | 59 | M | 1 | 6 | + | CR | CR | 8 | 10 |
| 10 | 44 | F | 2 | 6 | +½ | PR | PR | 7 | 8 |
| 11 | 63 | F | 0 | 5 | + | PR | PR | 15 | 16+ |
| 12 | 55 | F | 2 | 5 | + | SD | SD | 8 | 11 |
| 13 | 53 | F | 1 | 5 | +½ | CR | CR | 18 | 19 |
| 14 | 40 | F | 1 | 3 | + | SD | SD | 9 | 11 |
| 15 | 61 | M | 0 | 3 | + | PR | PR | 9 | 9+ |
| 16 | 41 | M | 1 | 5 | − | SD | PD | 6 | 7 |
| 17 | 63 | M | 2 | 4 | − | SD | PD | 8 | 10 |
| 18 | 54 | M | 1 | 4 | − | SD | PD | 5 | 5 |
| 19 | 49 | F | 2 | 4 | − | SD | PD | 4 | 5 |

RT, radiation therapy

**Table 3.** Combined modality treatment for locally advanced pancreatic cancer

| Reference | Patients (△) | Radiotherapy (in Gy) | Chemotherapy[a] | Median survival (months) |
|---|---|---|---|---|
| Moertel et al. [7] | 28 | 40 | 5-FU (during X) | 9.7 |
| | 31 | 60 | 5-FU (during X) | 9.3 |
| Newall et al. [10] | | 60 | FAM (post-X) | 10 |
| Schein et al. [12] | 26 | 45 (split) | FAM (1 cycle pre-X, 6 cycles post-X) | 13 + |
| Whittington et al. [18] | 19 | 63–70 | Varying 5-FU combinations | 12 |
| Mohiuddin et al. [9] | 54 | J-125 + 55 | FM + CCNU | 12.5 |
| GITSG [3] | 24 | 54 | SMF | 8 |
| Current series | 19 | 40 (split) | FAP (pre-X) | 14 |

[a] FU and F, 5-fluorouracil; A, Adriamycin; M, mitomycin C; P, cisplatin; X, irradiation; GITSG, Gastrointestinal Tumor Study Group

was seen in 14/19 patients; moderate patchy alopecia, in 1; and minimal hair loss, in 3 patients. Seven patients developed signs of mild neuropathy (WHO grade 1), and severe paraesthesias (WHO grade 2) developed in four. Irradiation combin with 5-FU was generally well tolerated. Nausea and vomiting was recorded in 5 of 15 patients: WHO grade 2 in 1 patient and grade 3 in 4; the latter was not dose-limiting but led to temporary hospitalization at the end of treatment. Haematologic toxicity was mild: one patient had a leucocyte count of WHO grade 3, and two had a platelet count of grade 2. In six patients a dose reduction (5-FU) was needed: in four patients due to a platelet count of $<100$ and in two because of increased paraesthesias shortly after 5-FU injection. The interval between the two cycles of radiation therapy never had to be delayed. No late radiation toxicity was seen and no toxic deaths occurred.

## Discussion

Treatment of locally advanced pancreatic cancer is at best palliative. There is still debate as to the value of combination chemotherapy in treating pancreatic cancer [11]. The Gastrointestinal Tumor Study Group (GITSG) failed to confirm the higher objective response rates seen in earlier studies with the FAM (5-FU, ADM, mitomycin C) and SMF (streptozotocin, mitomycin C, 5-FU) regimens [16]. In a randomized trial comparing 5-FU, 5-FU–ADM and FAM, the interval to disease progression, objective response rates and palliative effects were essentially equivalent for the three regimens [2].

Results of FAP therapy have previously been reported [4, 8]. These results are equal to those of other studies using a number of single drugs and drug combinations. In all cases, patients with advanced disease were treated. In the present investigation we treated only patients with locally advanced disease, and the drug doses used in our regimen were different. The doses of ADM and cisplatin were lower (40 and 30 mg/m$^2$ and 60 and 75 mg/m$^2$, respectively), in comparison with 50 mg/m$^2$ Adriamycin and 100 mg/m$^2$ cisplatin in our scheme. Although the adverse effects of the described schedule were severe, it is likely that the dose intensity was the cause for the comparatively good results in our study.

The results obtained in the present study compare favorably with those of studies using local treatment only: neutron beam irradiation [6], particle therapy [1], external beam [7, 18] and external beam and implant therapy [13]. The survival of patients in the current series also compares favorably with the results of combined modality treatment, as shown in Table 3. We did not observe an improvement of response after irradiation plus 5-FU. The patient group was too small and the methods of determination, too inexact to enable us to determine whether irradiation offers any benefit at all. Only a randomized trial evaluating the combined modality treatment vs the irradiation and 5-FU regimen using survival as the endpoint can give us a definitive answer.

Although the treatment duration of at least 7 months is a significant period in a disease with a short survival expectancy, the median duration of survival of 14 months justifies this long treatment period. Because no patient achieved further major response after three cycles and, for different reasons, only 10 of 19 patients could be treated with six cycles of FAP, in combined modality studies we now give radiation therapy after three cycles of chemotherapy. Furthermore, we conclude that combined modality treatment for locally advanced pancreatic cancer is feasible and warrants further testing.

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