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Adjuvant Combination Chemotherapy (AMF) Following Radical Resection of Carcinoma of the Pancreas and Papilla of Vater—Results of a Controlled, Prospective, Randomised Multicentre Study

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Between 1984 and 1987, 61 radically resected patients with carcinoma of the pancreas (n=47) or the papilla of Vater (n=14) were randomised either into postoperative adjuvant combination chemotherapy (AMF); 5-fluorouracil 500 mg/m², doxorubicin 40 mg/m², mitomycin C 6 mg/m² (n=30) once every 3 weeks for six cycles, or into a control group (no adjuvant chemotherapy) (n=31). The median survival in the treatment group was 23 months compared with 11 months (P=0.02, median test) in the control group, dependant on a survival benefit in the treatment group during the initial 2 years (P=0.04 generalised Wilcoxon). The long-term prognosis was the same with an identical survival after 2 years (P=0.10, power = 0.83). The observed 1, 2, 3 and 5-year survivals in the treatment group were 70, 43, 27 and 4% compared with 45, 32, 30 and 8 in the control group. 1 patient succumbed to sepsis probably attributable to chemotherapy. Cardiotoxicity and nephrotoxicity were recorded in 2 patients. These results suggest that adjuvant chemotherapy does postpone the incidence of recurrence in the first 2 years following radical surgery but increased cure rate was not observed.
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INTRODUCTION

THE INCREASING incidence of pancreatic carcinoma and the dismal prognosis represents a therapeutic challenge [1]. At present, radical surgery is the only modality with curative potential. The prognosis, however, is poor even in radically resected patients who have a 5-year survival of 0–18% [2–10]. Extended radical resections, therefore, have been introduced in order to improve long-term survival [11]. Such procedures are followed by a high complication rate [3, 5, 10, 12, 13]. In addition, they do not improve long-term survival [4, 6–10], with the exception of one study where a 5-year survival of 33% was reported [14]. The prognosis after resection of "early" pancreatic carcinoma seems to be a little more favourable and 5-year survival rates of 30% have been reported [15]. The prognosis after radical resection in carcinoma of the papilla of Vater is substantially better with reported 5-year survival rates within the range of 27–45% [2, 4, 10].

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Since it seems that a survival improvement is unlikely to be obtained by surgery alone, adjuvant chemotherapy should be tested. Cytotoxic chemotherapy in advanced pancreatic carcinoma has yielded response rates of up to 30–40% [16–20]. One single study has demonstrated improved survival after chemotherapy [21]. Radiotherapy administered before, during or after surgery has not been shown to have any beneficial effect on survival [13, 22–24]. A reported prospective randomised study of adjuvant combined radiation therapy and chemotherapy following radical resections, suggested significantly prolonged survival [25].

Here we report the results of a Norwegian prospective, randomised multicentre trial, designed to study whether adjuvant postoperative chemotherapy following radical resection of carcinoma of the pancreas or the papilla of Vater might improve long-term survival.

PATIENTS AND METHODS

38 Norwegian hospitals participated in a survey of all cancers of the pancreas and the papilla of Vater diagnosed between April 1984 and April 1987. 20 of these hospitals participated in the adjuvant chemotherapy study reported here.

Selection of patients

Only patients with histologically verified adenocarcinoma of the exocrine pancreas or the papilla of Vater were eligible after apparently radical pancreatic resections with tumour-free margins assessed by a pathologist review. Patients with endocrine tumours, cholangiocarcinoma, metastatic pancreatic tumours or cystadenocarcinoma were ineligible. The following inclusion criteria were also met: age below 75 years; Karnofsky index above 60; no cardiac diseases; normal renal function; S-bilirubin lower than 30 μmol/l 4–6 weeks postoperatively; no serious postoperative complications and informed consent.

Out of 110 patients with radical pancreatic resection (108 with Whipples resection or total pancreatectomy and 2 with radical distal resections), 61 patients were eligible for randomisation (Table 1). The clinical characteristics of the patients are given in Table 2. 3 radically resected patients, 1 with tumour-free margins and 2 without free margins had incorrectly been included in a study of the effect of tamoxifen in unresectable pancreatic carcinoma [26].

Surgical treatment

Each participating hospital followed their own strategy for radical surgery, total pancreatectomy or pancreatico–duodenal resection a.m. Whipple with or without splenectomy. Tumours with regional lymph node metastases that could be resected *en bloc* with the primary tumour were considered eligible for the study. Distal pancreatic resections reported as radical were also included. The original tumour node metastases (TNM) classification for carcinoma of the pancreas or papilla of Vater was recorded according to the proposed classification rules for pancreatic carcinoma [27], but was afterwards revised according to the approved 1987 UICC classification for carcinoma of the pancreas and papilla of Vater [28].

Chemotherapy

Adjuvant combination chemotherapy, AMF, was administered as a combination of doxorubicin (Adriamycin^R, Farmitalia Carlo Erba) 40 mg/m^2, mitomycin C (Bristol-Myers Comp.) 6 mg/m^2, and 5-fluorouracil (F. Hoffman-La Roche AG) 500 mg/m^2. Doxorubicin and 5-fluorouracil were given directly into

Table 1. Reasons for exclusion before randomisation

	No. of patients
Preoperative cytostatic chemotherapy	1
Age over 75 years	7
Drug addict	1
Patient refusal	6
Postoperative death	12
Serious postoperative complications or heart disease	4
Margin of resected specimen not free	4
s-Bilirubin > 30 μmol/l	1
Incorrectly included in tamoxifen study	1
Unknown	9
Total	46

Table 2. Characteristics of patients

	AMF (n=30)	Control (n=31)		Ineligible (n=46)
Age (years)				
Mean	64.3	58.9		68.1
Median	66.5	62	P=0.009	67
Range	36–75	40–72		50–81
Karnofsky's index preoperatively				
Mean	85.7	85.5		79.3
Median	90	80		80
Range	70–100	70–100		50–100
Sex				
Male	16	18		26
Female	14	13		20
Tumour site				
Papilla	7	7		9
Head	20	23		29
Body	2	1		5
Tail	1	0		3
Surgical procedure				
Total pancreatectomy	2	3		1*
Total pancreatectomy with splenectomy	7	8		7
Whipple's operation	20	19		34
Whipple's operation with splenectomy	0	1		1
Distal resection	1	0		1
No. with complications after surgery**	16	18		46
TNM stage				
I	22	19***		24***
T1NO	9	11		
T2NO	13	8		
II	1	1		8
III	7	10		11
IV	0	0		2

*Missing data for 2 cases.
**Summary of 11 recorded types of complications.
***Missing data for 1 case.
Discrete variables compared between the three groups. Continuous variables compared between AMF and control group.
P values given for significant differences.

Table 3. Dosage adjustment according to haematological parameters before each scheduled course of chemotherapy with AMF

Leucocyte particle concentration (×10⁹/l)	Thrombocyte particle concentration (×10⁹/l)	5-Fluorouracil (%)	Doxorubicin (%)	Mitomycin C (%)
> 3.5	> 125	100	100	100
> 3.0	> 100	75	75	75
> 2.5	> 75	50	50	50
> 2.5	< 75			Mitomycin omitted
< 2.5	< 75	Treatment is postponed for 1 week. If the same level is found after 2 weeks, AMF is discontinued.		

the tubing of a running intravenous saline infusion during 3–5 min. Then mitomycin C was added to the saline bag and infused over 30–45 min. The 1-day courses were repeated every 3 weeks for a total of six courses starting within 6 weeks after surgery. Most patients received chemotherapy as out-patients.

Leucocyte and thrombocyte counts were obtained immediately prior to each course, and appropriate drug reductions were performed based upon haematological toxicity (Table 3). Doxorubicin was omitted if cardiac complications were seen. Mitomycin C was omitted if renal or pulmonary complications developed, or if a diagnosis of microangiopathic haemolytic anaemia was made. Doxorubicin and 5-fluorouracil were reduced to 50% if serious gastrointestinal symptoms developed: stomatitis grade 3–4, nausea or vomiting grade 4, diarrhoea grade 3–4 (WHO). All chemotherapy was discontinued after vomiting grade 4 or diarrhoea grade 4, despite conventional antiemetic or antidiarrhoea therapy.

Randomisation

The actual time of randomisation should be as close as possible to the start of chemotherapy which preferably should be within 4 weeks after surgery but may be postponed to 6 weeks to fulfil trial entry criteria. After informed consent, all patients were included in the trial by a telephone call to the trial headquarters. The eligibility criteria were first checked by a secretary. Balanced randomisation, stratified according to sex, was used to ensure equal numbers of patients in the two groups. Information on treatment allocation based on the randomisation list was not available for participants. No information on trends in survival difference between the two groups was given during the study. Because of expected side-effects of chemotherapy, we found it impossible to blind the adjuvant therapy, hence placebo infusion was not given.

Statistics

The therapeutic goal was to increase median survival by a factor of two from 8 to 16 months, or the 1-year survival from 20 to 40%. Based on $\alpha = 0.05$ and $\beta = 0.10$, we estimated that 86 patients should be included in order to detect such differences. All time intervals were measured from the date of randomisation to either death or the date of the last follow-up. To compare the accepted and randomised patients with the ineligible patients, the survival of the last group was measured from 30 days after surgery. Non-censored variables were compared by χ^2 statistics. Survival curves were calculated by the Kaplan–Meyer method [29]. Survival in the two groups was compared with the median test, the log-rank test [30] and Gehans generalised Wilcoxon test [31]. A two-tailed test with a P value < 0.05 was regarded as statistically significant. Trends were defined as P values between 0.05 and 0.10. Computations were performed by the BMDP (BMDP Statistical Software, Los Angeles, California, USA) Statistical Program Package [32] implemented on the Univac 1100 (Sperry-Univac, Salt Lake City, Utah, USA) computer of the University of Bergen.

Withdrawals

All randomised patients were analysed according to the "intention to treat" principle. 1 patient in the AMF group had to be considered as missing in the survival analysis since he died the same day he incorrectly was randomised.

Ethical considerations

Before randomisation, oral informed consent was obtained from eligible patients after written information about the aim of the study, the treatment with chemotherapy, the side-effects and the randomisation procedure. The official Regional Ethics Committee of Western Norway approved the trial.

Follow-up

Patients in the chemotherapy group were evaluated before each scheduled course of AMF. Appropriate history, physical examination, body weight, clinical performance according to Karnofsky's index [33], laboratory tests and side-effects of the previous course were recorded on standardised forms which were submitted to the study headquarters after each course. Control patients were seen at the local out-patient clinic every third month for 2 years, then every 6 months for up to 5 years or until disease progression made out-patient visits impossible. Patients in the AMF group were seen after similar time intervals. Follow-up included clinical performance, postoperative complications, any adverse effects of theapy as well as survival. After each follow-up the results were recorded on special forms and submitted to the study headquarters. In addition, information concerning patient survival was obtained from the Cancer Registry of Norway until 1 January 1990, the end point of follow-up in the study.

RESULTS

The median survival was 23 months in the AMF arm compared with 11 months in the control group (median test, $P=0.02$), Table 4. Despite this initial survival improvement, the long-term survival (5 years) was not significantly changed

Table 4. Observed survival in adjuvant chemotherapy group (AMF), in control group and in excluded patients after radical resection of carcinoma of the pancreas or papilla of Vater

Time (years)	AMF ($n=29$) % of patients surviving	Control ($n=31$) % of patients surviving	Ineligible ($n=35$) % of patients surviving
1	70	45	54
2	43	32	20
3	27	30	9
4	16	24	3
5	4	8	3

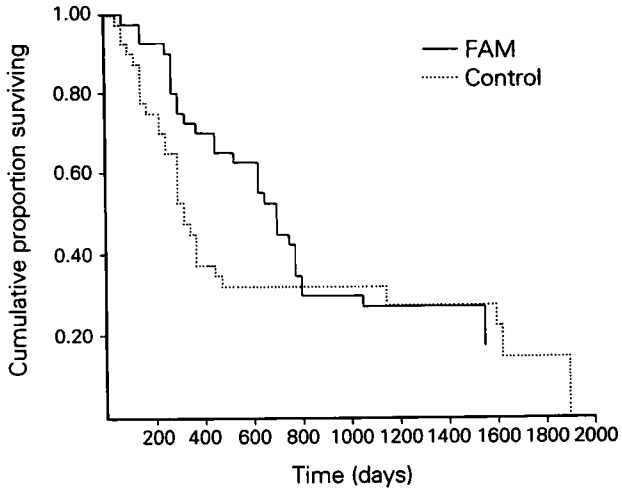

Fig. 1. Life table analysis of survival for all randomized patients, (___) AMF group (n=29), (. . .) control group (n=31); generalised Wilcoxon P=0.099; power=0.83; median test P=0.021.

(P=0.10, power 0.83, generalised Wilcoxon test; Fig. 1). 22 of 29 patients (76%) in the chemotherapy group and 25 of 31 patients (81%) in the control group died of their malignant disease during the entire observation period. However, there was a significantly different survival during the first 2 years (generalised Wilcoxon, P=0.04). 7 patients in the AMF group, (6 with carcinoma of the papilla of Vater and 1 with carcinoma of the head of pancreas) had a survival of 38–67.5 months after entry, compared with 6 patients in the control group (4 with carcinoma of the papilla of Vater and 2 with carcinoma of the head of pancreas). The observed 5-year survivals in the AMF and control groups were 4 and 8%, respectively (P=0.6), which were not statistically significant.

The median survival of the 35 ineligible patients who survived at least 30 days postoperatively, was 13.3 months. The observed 1, 3 and 5-year survival times for these patients were 54, 9 and 3%, respectively. 4 of these patients were still alive after 34–70.5 months. 1 of these patients survived for 5 years (Fig. 2).

Treatment compliance and toxicity

Only 24 of the 30 patients who were randomised to AMF treatment actually received such therapy: 1 patient died on the same day as randomisation was undertaken, 2 refused treatment, 1 had a Karnofskys index below 60, and 2 dropped out for unknown reasons. 7 patients started therapy within 4 weeks postoperatively, 15 between 4 and 6 weeks and 2 patients after 6 weeks. Only 13 patients completed all six scheduled courses. 2 patients refused further therapy after the first course. Treatment was discontinued due to side-effects in 5 patients. Gastrointestinal toxicity—mainly grade 1—was the major problem (Table 5). The haematological toxicity was moderate with a median leucocyte and thrombocyte count before each therapy course within normal values. At the first course, 16 of 22 patients (73%; missing data in 2 cases) were hospitalised, compared with 6 of 13 patients (46%) during the last course.

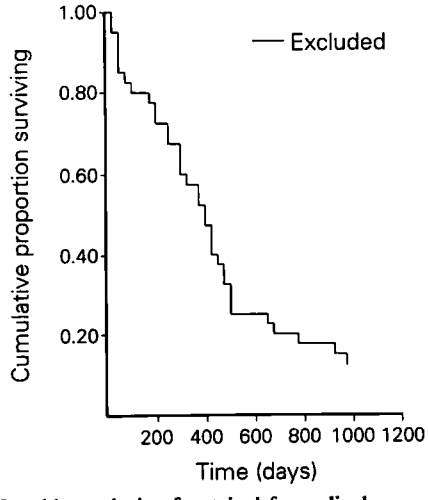

Fig. 2. Life table analysis of survival for radical operated patients excluded before randomisation (n=35). Time is measured from day 30 after operation.

Patient clinical performance as measured by Karnofsky's index was stable during the treatment period. The median body weight however, was reduced by 7 kg. Cardiotoxicity was observed in 2 patients and nephrotoxicity in 2 patients. 11 patients (50%) developed alopecia. A woman, aged 71 years, died from sepsis and renal insufficiency after the third course, probably attributable to the AMF chemotherapy. During chemotherapy 4 other patients in the AMF group had sepsis but survived this complication. During the same time interval, 4 control patients died. During the first follow-up year, 4 of 18 patients in the treatment group complained of nausea and vomiting after 3 months of follow-up compared with none (0 of 18) in the control group (P=0.06). Otherwise, the two groups had a comparable clinical performance for up to 12 months, with a median Karnofsky's index of 80 and 90 at 3 months in the treatment and control groups, respectively. Afterwards, the median Karnofsky's index was 90 in both groups.

DISCUSSION

The aim of this trial to double the median survival after radical resection for carcinoma of the pancreas and the papilla of Vater, was in a way achieved by a moderately toxic combination chemotherapy regimen using doxorubicin, mitomycin C and 5-fluorouracil. There was no long-term improvement of survival as previously reported in a non-randomised pilot study with a historical control group [34]. The 3-year survival rates after curative resection with and without FAM are 24 and 28%, respectively, compared with 3-year survival rates of 27 and 30% in the present study. A GITSG study has evaluated the role of radiation and single drug chemotherapy (5-FU) beginning with each course of radiation and continued on a once-weekly basis for 2 years or until recurrence [25]. The survival benefit observed in this study is nearly the same than that obtained in the GITSG study where the median survival increases from 10.9 to 21 months. This study was confirmed by a second phase II trial involving 30 patients with the same treatment with radiotherapy and 5-FU and the median survival is comparable (18 months) [35]. As the numbers of these two studies conducted by the GITSG are small, these results need to be confirmed; an ongoing prospective randomised trial is opened for randomisation in the Gastrointestinal Tract Cancer Cooperative Group of EORTC (Protocol 40891) comparing radiotherapy and 5-FU treatment vs. no treatment.

Most surgeons are reluctant to enter patients into adjuvant chemotherapy programs following radical resection for pancreatic carcinomas because of the poor prognosis and poor prospects of the chemotherapy. We had to stop the patient accrual after 3 years. Kalser and Ellenberg also noted slow patient accrual. Although designed to be relatively tolerable, the AMF regimen appeared to be toxic given to this type of patients, as also noted

Table 5. Follow-up during courses of chemotherapy and toxic reactions

Category	No. of patients (n=24) AMF course number 1	2	3	4	5	6
Hospitalised	16	9	10	6	6	6
Ambulatory	6	9	7	8	7	7
Haematological leucocytes ($\times 10^9$/l)						
> 3.5	18	15	10	7	9	5
3.0–3.5	0	1	1	2	0	4
2.5–3.0	0	1	1	3	4	1
< 2.5	0	0	3	1	0	1
Thrombocytes ($\times 10^9$/l)						
> 125	16	17	13	12	12	10
100–125	1	0	0	0	0	0
75–100	0	0	1	0	1	0
< 75	0	0	0	0	0	0
Gastrointestinal grade*						
0	10	10	8	5	5	2
1	5	6	3	4	5	5
2	3	0	1	0	1	3
3	0	1	3	1	0	0
4	0	0	0	0	1	0
Cardiovasculary						
Yes	0	0	1	1	0	0
No	18	17	14	10	12	10
Bleeding						
Yes	0	0	0	0	0	0
No	16	17	14	10	12	10
Sepsis						
Yes	0	1	2	1	0	0
No	16	16	13	9	12	10
Renal						
Yes	0	0	2	0	0	0
No	16	17	12	10	12	10
Others**						
Yes	5	4	5	2	1	1
No	11	12	10	8	11	9
Change due to side-effect						
Increased interval	1	1	3	3	1	0
Dose reduction	2	3	1	5	4	5
Discontinued						
Yes	0	1	2	0	1	1
No	11	12	9	5	7	5
Karnofsky's index***						
Mean	82.2	81.5	80.6	83.8	82.9	80.8
Median	80	85	80	90	85	80
Range	60–100	50–100	40–100	60–100	50–100	70–100
Body weight (kg)						
Mean	61.1	60	55.9	56.2	54.3	55.7
Median	60	60	55.5	53	52	53
Range	34–79	34–78	31–78	42–75	41–72	46–70

*International criteria of WHO.
**See Table 6.
***Before start of each course.

Table 6. Other side-effects in AMF treated group

Side-effect	No. of patients
Alopecia	11
Epileptic fit from hypoglycemia	1
Wound abscess	1
Vertigo	1
Exanthema	1
Anorexia	1
Deep vein thrombosis	1
Crural oedema	1
Persistent nausea	1
Total	19

by Splinter *et al.* [34]. 1 of our patients actually died from causes that might be attributed to chemotherapy and 4 other patients had septicaemia but survived this complication. This contrasts with the report by Smith *et al.* [16] and Bitran *et al.* [18] who used the same regimen as Splinter *et al.* [34] for non-resectable patients. They concluded that even a more intense FAMregimen used in advanced pancreatic carcinoma is well tolerated. In unresectable patients the combination FAM regimen was clearly more toxic than 5-FU alone [19]. In fact, Splinter noted that the standard FAM regimen was so badly tolerated that only 1 patient resumed some of his normal activity during chemotherapy. In contrast, our moderate-dose FAM regimen called AMF regimen did not reduce the median Karnofsky's index after each course below a median of 80–90 and only 4 patients were unwilling to fulfil all scheduled courses. The subjective side-effect after chemotherapy was also transient since the rate of nausea and vomiting only differed at 3 months postoperatively. At later time intervals no differences were found between the two groups. Our AMF regimen, although still toxic, might be more acceptable for the patient than the standard FAM as reported by Splinter *et al.* [34], but still without loss of the antitumour effect.

Ineligible patients had a survival curve identical to the control group, substantiating an initial true beneficial influence on survival from adjuvant chemotherapy. We did not achieve our goal to include 86 patients in this study, which reduced the power of the test statistics from 0.9 to 0.83 which consequently increases the risk of the insignificant long-term result to be a type II error. The chemotherapy arm did not include more patients with more favourable tumour characteristics (T1a vs. T1b, T1 vs. T2) than the control arm.

CONCLUSION

This study demonstrates that adjuvant chemotherapy is toxic but feasible and does postpone the incidence of recurrence at least in the first 2 years after curative resection of carcinomas of pancreas or papilla of Vater. Further studies using combination chemotherapy in advanced pancreatic cancer should aim at finding even more efficient regimens that can be tested in the adjuvant setting.

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