PAPERS AND ORIGINALS

Chemotherapy in pancreatic cancer: results of a controlled, prospective, randomised, multicentre trial

C N MALLINSON, M O RAKE, J B COCKING, C A FOX, M T CWYNARSKI, B L DIFFEY, G A JACKSON, J HANLEY, V J WASS

Summary and conclusions

Forty patients with inoperable pancreatic cancer were included in a prospective, randomised, controlled trial of multiple chemotherapy. The survival of 19 untreated control patients was compared with that of 21 patients who received an initiation course of intravenous fluorouracil, cyclophosphamide, methotrexate, and vincristine given over five days followed by intravenous fluorouracil and mitomycin given over three or five days at six-week intervals thereafter. Median survival in treated patients was 44 weeks, which was significantly longer than the nine weeks seen in controls. In patients without metastases median survival was 48 weeks in the treated group and 12 weeks in controls. In patients with metastases it was 30 weeks in treated patients and seven weeks in controls.

The treatment was well tolerated and seemed to confer a significant prolongation of survival, comparing favourably with previous reports of chemotherapy with or without radiotherapy. If the results are confirmed this regimen may be useful in district general hospital practice.

Introduction

The five-year survival of patients with pancreatic cancer is about 1%, largely because visible or microscopical spread of tumour has occurred in 99% of patients by the time of diagnosis, including those in whom the primary tumour can be resected.¹ By 1975 the investigation of treatments that were alternative or adjuvant to surgery suggested that chemotherapy, radiotherapy, and combinations of the two showed some promise in reducing tumour size in pancreatic cancer. The best combinations of drugs and their effect on the duration of survival were not certain.¹ For this reason we started a prospective, controlled, randomised trial of multiple chemotherapy in patients with inoperable carcinoma of the pancreas using the drugs which gave most promise at the time. Early results suggested that the treatment prolonged survival² and this impression was confirmed at the end of the study by the results presented below.

Patients and methods

Patients aged 35 to 75 years with unresectable pancreatic cancer diagnosed at laparotomy were included in the trial. Patients were excluded if they were unable to visit the outpatient clinic regularly; if they showed impaired renal function, unrelievable gastrointestinal obstruction, neutropenia (white cell count less than $3.5 \times 10^9/l$), or thrombocytopenia (platelet count less than $80 \times 10^9/l$); or if they had already received radiotherapy or cancer chemotherapy.

Relatives and family doctors of the patients were informed of the diagnosis but the patients themselves were not necessarily aware of the finding of a malignant tumour.

The control and treatment groups were well matched for sex, age, duration of symptoms before diagnosis, tumour load estimated at laparotomy, palliative operation, and their condition and body weight at the start of treatment (table I).

Drug regimen—Chemotherapy was started after sutures were removed and at least 10 days after laparotomy or the end of any postoperative infection. Treatment was always started within one month of diagnosis. Patients were randomised into treatment and control groups 24 hours before treatment started and received one of two schedules of management which were known to the treating physician. The control group received analgesics and other supportive

Lewisham Hospital, London SE13

C N MALLINSON, MB, FRCP, consultant physician

C A FOX, MD, MRCP, research fellow

J HANLEY, MB, MRCP, research registrar

Kent and Canterbury Hospital, Canterbury, Kent CT1 3NG

M O RAKE, MB, FRCP, consultant physician

M T CWYNARSKI, MB, MD research fellow

B L DIFFEY, PHD, MINSTP, senior physicist

G A JACKSON, research assistant

V J WASS, MB, BS, research fellow

Isle of Thanet District Hospital, Ramsgate Wing, Ramsgate, Kent

J B COCKING, MB, FRCP, consultant physician

treatment at regular clinic visits but no placebo. The treatment group received an initiation course of fluorouracil, methotrexate, vincristine, and cyclophosphamide, given in hospital over five days. All drugs were given intravenously as separate bolus injections followed by 5 ml of normal saline in the doses and order shown in table II. Follow-up treatment consisting of intravenous fluorouracil, 10 mg/kg body weight, and mitomycin, 100 µg/kg body weight, was given, also by intravenous bolus injection, daily on five consecutive days. This was started four weeks after the end of the initiation course and repeated every six weeks until death or for two years.

Assessment—A standardised record was kept of the duration of

TABLE I—Details of patients with pancreatic cancer at the time of entry into the trial

	Controls (n = 19)	Treatment group (n = 21)	Total (n = 40)
No of men	10	12	22
No of women	9	9	18
Median age (years)	66.9	63.4	
No with history > 6 months	16	16	32
No with history ≤ 6 months	3	5	8
No with only local disease	11	14	25
No with liver metastases visible	7	5	12
No with liver and distant metastases	1	2	3

TABLE II—Drug regimen used in the initiation course. Figures in parentheses show dose when patient's weight fell outside 60-80 kg range

Day	Cyclophosphamide	Fluorouracil	Vincristine	Methotrexate
1	300 mg	500 mg		20 mg
2		500 mg	1 mg	
3		500 mg		
4		500 mg		20 mg
5	300 mg (4.5 mg/kg)	500 mg (7.5 mg/kg)	1 mg (0.02 mg/kg)	

TABLE III—Median survival of control and treated patients with pancreatic cancer in relation to histological confirmation and tumour load. Results are numbers of patients

Category and group	No of patients	Median survival (weeks)	p value
All patients:			
Control	19	9	0.0006
Treated	21	44	
Histology confirmed:			0.006
Control	11	7	
Treated	15	31	
Histology unconfirmed:			0.002
Control	8	12	
Treated	6	48	
Local tumour only:			0.001
Control	11	12	
Treated	14	48	
Hepatic metastases:			0.048
Control	8	7	
Treated	7	33	

TABLE IV—Pancreatic cancer: comparison of the four commonest symptoms. Three patients were omitted because of incomplete data

	Pain		Nausea		Vomiting		Diarrhoea	
	Treated	Control	Treated	Control	Treated	Control	Treated	Control
No of patients in group	21	16	21	16	21	16	21	16
No (%) of patients ever experiencing symptoms	19 (91)	11 (69)	17 (81)	7 (44)	15 (71)	7 (44)	11 (52)	5 (31)
Total No of patient visits	125	38	125	38	125	38	125	38
Mean symptom score per visit	0.50	0.79	0.41	0.50	0.31	0.47	0.35	0.35

the symptoms present before diagnosis and the extent of tumour found at laparotomy. The results of clinical examination were also noted on inclusion in the trial and at the regular follow-up visits that all patients made. The following factors were scored 0-4 depending on severity: pain, nausea, vomiting, stool frequency, hair loss, analgesic requirement. Body weight was recorded, the Karnofsky score assessed,³ and well-being scored 0-4 by the patient. Blood was taken to estimate haemoglobin, full cell count, erythrocyte sedimentation rate, and concentrations of urea, bilirubin, alkaline phosphatase, alanine and aspartate aminotransferases, and gamma glutamyl-transferase. Radioisotopic liver scans were carried out every 18 weeks.

Results

By the end of three years 40 patients had been admitted to the trial, 21 in the treated group and 19 in the control. Seventeen of the controls and six of the treated patients died before six months. All but one patient died within two years. No patient withdrew from the trial or was lost to follow-up. Survival in the treated and control patients was compared by the log-rank test recommended by Peto *et al.*⁴ As shown in the figure, the median survival of the treated patients was 44 weeks and that of the controls nine weeks, a highly significant difference ($p=0.00006$).

Survival curve for treated and control patients with pancreatic cancer. One patient in the treated group survived for two years.

Table III shows the median survival in patients with and without histological confirmation of the diagnosis. In both of these groups the treated patients survived significantly longer than the controls. Within the treated group of patients there was no significant difference in median survival between those with histologically confirmed diagnoses and those without ($p=0.42$), and the same held for the control patients ($p=0.55$). Patients with metastatic tumour visible at laparotomy had a shorter median survival than those without, but treated patients survived significantly longer than controls even when metastases were present (table III).

Non-parametric statistical analysis of the clinical, biochemical, and haematological measurements assessed at different intervals in

the two groups showed only a significant increase in nausea in the treated patients ($p=0.001$). A wide variation in these indices was seen (details available on request). Table IV shows the evaluation of the four commonest symptoms corrected for duration of survival. This correction was necessary since the length of survival in the two groups was so different. These results suggest that the controls had at least as much nausea, vomiting, and pain and no less diarrhoea than treated patients. The chemotherapeutic regimen was in fact well tolerated, and nausea was short-lived and controllable by oral antiemetics. Haematological data showed that no patient had a white cell count below $2 \times 10^9/l$ and only three treated patients had less

than $40 \times 10^9/l$ platelets on one occasion each. No patient had purpura or significant sepsis associated with the treatment. Mild thinning of the hair was seen in six patients.

Discussion

The median survival of 44 weeks in the treated patients in this study is the longest reported survival in any prospective controlled trial of chemotherapy, with or without radiotherapy, in inoperable pancreatic cancer. The median survival of patients treated by surgical resection is only 16 weeks longer.¹ The median survival of nine weeks in untreated patients was obviously and significantly shorter and is similar to that in several other reports of patients receiving no treatment or ineffective drugs.¹⁻⁶ We conclude that the improved survival was due to the chemotherapy since the patients in the two groups were well matched for those factors which are known to affect prognosis in this disease.¹

The difference in survival of the two groups may have also been influenced by hidden bias. It is notoriously difficult to assess at laparotomy the extent of macroscopic and microscopic spread from pancreatic cancer. This might have influenced the survival results if the spread in the control patients was more extensive than in the treated. Obviously serial observations of a measurable marker lesion in each case would have provided ideal corroborative evidence of the effect of chemotherapy, but such lesions were not found in a single case. The degree of malignancy of the tumours was not measured but would not, on existing evidence, account for a difference in median survival of more than two months between the two groups. The longest median survival, seen in patients without metastases, was about six weeks longer than that in comparable patients treated with fluorouracil and radiotherapy.⁷ Nevertheless, median survival in patients with metastases was also prolonged compared with that in controls and compared well with results in similar patients in phase II studies of more complicated triple regimens in which either streptozotocin⁸⁻⁹ or adriamycin¹⁰⁻¹¹ was added to fluorouracil and mitomycin-C.

A few patients did not have their condition histologically confirmed because at the start of the trial many referring surgeons were reluctant to biopsy primary tumours. All but one of these patients died within two years, treated or not, and their course was very similar to that of histologically confirmed patients. This suggests that it is justifiable to include them in the results.

Fluorouracil and mitomycin were combined in this regimen because of the existing evidence of their modest effectiveness as single agents.¹ Since our initial results were published² two reports of the two drugs in combination have appeared¹²⁻¹³ and both agents are included in most chemotherapeutic regimens on trial at present.¹⁴ The quadruple initiation regimen had shown promising results in reducing hepatic metastases from gastrointestinal adenocarcinomas.¹⁵ Since then methotrexate in the dose used and cyclophosphamide have not proved effective agents in pancreatic cancer and vincristine has not been tested further. The toxic effects of fluorouracil and mitomycin are well recognised: both are toxic to bone marrow, causing neutropenia and thrombocytopenia, and both induce nausea and vomiting, alopecia, and oral ulceration. Mitomycin has been reported as causing pulmonary, hepatic, and renal damage as well. The dose regimen used in this study was intended to prevent side effects so far as possible in a comparatively elderly group of patients who were being treated palliatively rather than in the expectation of a cure. Perhaps for this reason the incidence of side effects was low and largely confined to reversible bone marrow depression and transient nausea. Higher doses would be expected to be more toxic, particularly in this group of patients, but might not be more effective.

This study shows a clear increase in survival in patients on this regimen of chemotherapy. Should these results be confirmed this combination of drugs seems to be acceptable to the patients and feasible in a district general hospital.

This trial would not have been possible without the generous support of the consultant surgeons who referred cases to us and the staff of the departments of pathology and nuclear medicine, who carried out the investigations; we thank them most gratefully. Our thanks are also due to Mrs Sue Case for secretarial help and Miss Debbie Main for technical help. The entire trial was supported by a grant from the South-east Thames Regional Health Authority Locally Organised Clinical Research Fund.

Requests for reprints should be addressed to Dr C N Mallinson, Lewisham Hospital, London SE13.

References

- Carter SK, Comis RL. The integration of chemotherapy into a combined modality approach for cancer treatment. V. 1. Pancreatic adenocarcinoma. *Cancer Treat Rev* 1975;2:193-214.
- Mallinson CN, Rake MO, Fox CA, Cwynarski MT, Cocking JB, Jackson GA, Diffey BL. *Gut* 1976;17:826-7.
- Karnofsky DA. Meaningful clinical classification of therapeutic responses to anti-cancer drugs. *Clin Pharm Ther* 1961;2:709-12.
- Peto R, Pike MC, Armitage P, et al. Design and analysis of randomised clinical trials requiring prolonged observation of each patient. *Br J Cancer* 1977;35:1-39.
- Moertel CG, Douglass HO, Hanley J, Carbone PP. Treatment of advanced adenocarcinoma of the pancreas with combinations of streptozotocin plus 5-fluorouracil and streptozotocin plus cyclophosphamide. *Cancer* 1977;40:605-8.
- Schein PS, Lavin PT, Moertel CG, et al. Randomised Phase II clinical trial of adriamycin, methotrexate and actinomycin-D in advanced measurable pancreatic carcinoma: a Gastrointestinal Tumour Study Group Report. *Cancer* 1978;42:19-22.
- Moertel CG, Lokish JJ, Childs DS Jr, Lavin PT. An evaluation of high dose radiation and combined radiation and 5-fluorouracil therapy for locally unresectable pancreatic carcinoma. *Proceedings of the American Association of Cancer Research and American Society of Clinical Oncology* 1976;17:244.
- Abderhalden RT, Bukowski RM, Groppe CW, Hewlett JS, Weick JK. Streptozotocin, 5-fluorouracil with and without mitomycin-C in the treatment of pancreatic adenocarcinoma. *Proceedings of the American Association of Cancer Research and American Society of Clinical Oncology* 1977;18:301.
- Wiggins RG, Woolley PV, Macdonald JS, Smythe T, Winston PA, Ueno W, Schein PS. Phase II trial of streptozotocin, mitomycin-C and 5-fluorouracil in the treatment of advanced pancreatic cancer. *Cancer* 1978;41:387-91.
- Smith FP, Macdonald JS, Woolley PV, et al. Phase II evaluation of FAM 5-fluorouracil (F), adriamycin (A), and mitomycin-C (M) in advanced pancreatic cancer. *Proceedings of the American Association of Cancer Research and American Society of Clinical Oncology* 1979;20:415.
- Bitran JD, Dresser RK, Kozloff MF, Billings AA, Shapiro CM. Treatment of metastatic pancreatic and gastric adenocarcinomas with 5-fluorouracil adriamycin and mitomycin-C. *Cancer Treatment Reports* 1979;63:2049-51.
- Krauss S, Sonoda T, Solomon A. Treatment of advanced gastro-intestinal cancer with 5-fluorouracil and mitomycin-C. *Cancer* 1979;43:1598-1603.
- Buroker T, and 15 other authors. 5-FU infusion with mitomycin-C vs 5-FU infusion with methyl CCNU in the treatment of advanced upper gastro-intestinal cancer. A South-West Oncology Group Study. *Cancer* 1979;44:1215-21.
- Davis HL, Von Hoff DD, Rozenzweig M, Handelsman H, Soper WT, Muggia FM. In: Staquet MJ, ed, *Randomised trials in cancer: a critical review by sites*. New York: Raven Press, 1978:147-230.
- Hanham IWF, Newton KA, Westbury G. Seventy-five cases of solid tumours treated by a modified quadruple chemotherapy regimen. *Br J Cancer* 1971;25:462-78.

(Accepted 20 October 1980)

ONE HUNDRED YEARS AGO A summons was on Saturday applied for, at the Marlborough St Police-Court, against a Miss Houghton, practising as a "healing clairvoyante" and spirit medium, for obtaining 2s 6d for pills, which she pretended had been spiritualistically prescribed for a person suffering from neuralgia, which turned out to be formed of sugar only. The summons was granted. So much is there in a name. The pills were apparently homoeopathic globules; and, had this incautious person invoked the name of Hahnemann only, and spoken mysteriously of potentising by dilution, and dynamising by trituration, she might have risen to much honour and profit. (*British Medical Journal*, 1880.)