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Clinical trials

Chemotherapy in advanced gastric cancer: a controlled, prospective, randomised multi-centre study

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

From the Kent and Canterbury Hospital, Canterbury, Lewisham Hospital, London, and Isle of Thanet District Hospital, Ramsgate, Kent

SUMMARY Seventy-six patients with advanced gastric adenocarcinoma were studied in a prospective, randomised, controlled trial using vincristine, methotrexate, cyclophosphamide, and 5-fluorouracil in an initiation course and mitomycin-C with 5-fluorouracil as maintenance therapy. Thirty-seven patients were inoperable and 39 had the primary tumour resected with histological evidence of residual disease. Survival in the inoperable group was short and showed no significant difference between treated and control patients. The median survival times for treated and control groups were 9.5 and 9.0 weeks respectively. In the resected patients there was no difference in ultimate overall survival between the groups but up to 20 weeks there was a suggestion that the probability of survival in treated patients was higher ($P=0.06$). The patients were well-matched and it is concluded that chemotherapy has had an early effect but that a further trial with more detailed stratification, particularly of staging and histological grade, is needed. No patient received treatment for longer than two years and unacceptable toxicity occurred in only two patients. Nausea occurred more frequently in the treated group but was short-lived and clinically manageable.

Carcinoma of the stomach has a poor prognosis with an overall five-year survival rate from time of diagnosis ranging from 5% (Brookes *et al.*, 1965) to 19·4% (Hawley *et al.*, 1970). Attempts at prolonging survival by chemotherapy have been successful in only one recent study (Moertel *et al.*, 1976). Transient remission and tumour regression, however, have been reported with the single agents 5-fluorouracil and mitomycin-C (Moertel, 1976; Imanaga and Nakazato, 1977; Nakajima *et al.*, 1978). The combination of these two therapeutic agents and also studies with the nitrosoureas and adriamycin have been shown to produce regression and remission in a proportion of patients (Comis and Carter, 1974; Vaitkevicius *et al.*, 1975; MacDonald *et al.*, 1976; Priestman, 1978).

In 1974 we started a prospective, randomised, controlled trial of combination chemotherapy in 76 patients—37 'inoperable' and 39 with 'resected' gastric carcinoma. The findings after two years were encouraging and have been reported elsewhere (Rake *et al.*, 1976). Since then a larger multi-centre trial has been established based on London and Birmingham. This paper reports the final outcome of the original trial and shows that the initial trends in favour of chemotherapy have disappeared.

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Methods

PATIENTS

Patients between the ages of 35 and 75 years with histologically-proven gastric cancer in whom the tumour could not be totally removed were included in the trial. They were divided into two groups: those in whom the primary tumour could not be removed (inoperable) and those in whom the primary tumour was removed but histological evidence of residual disease remained (resected).

Patients were excluded from the trial if they were physically or mentally unable to co-operate with the treatment of cytotoxic drugs or with repeated clinical assessments, if they showed impaired renal function, unrelievable gastrointestinal obstruction, neutropenia (WBC $<3{\cdot}5\times10^9$/l ($<3{\cdot}5\times10^3$/mm^3)], thrombocytopenia [platelet count $<80\times10^9$/l ($<80\ 000$/mm^3)), or if they had received previous radiotherapy or

Table 1 *Findings in 37 patients in 'inoperable' group*

		Control	Treatment	Total
Total		18	19	37
Females		9	10	19
Males		9	9	18
Mean age (range) (yr)		67·4 (50–75)	65·4 (50–75)	
Length of history (m)	>6/12	3	3	6
	<6/12	15	16	31
Liver metastases	Present	6	8	14
	Absent	8	6	14
	Not known	4	5	9
Lymph nodes	Involved	12	12	24
	Not involved	2	2	4
	Not known	4	5	9
Distant metastases		2	1	3

chemotherapy.

The relatives and general practitioners of the patients were informed of the diagnosis but the patients themselves were not necessarily always aware of the finding of malignant tumour.

The control and treatment groups were well-matched for sex, age, and approximate tumour load as shown in Tables 1 and 2. The duration of the history in patients with 'inoperable' tumour was less than six months in 31 of the 37 patients (14 showed evidence of hepatic metastases, and three of distant metastases.

In patients with 'resected' tumour there was a preponderance of males. There was no difference in age between the groups and the length of history was similar. Liver metastases were present in five patients—four in the control and one in the treatment group. Lymph node spread was evident in 34 of the 39 patients and distant metastases were present in one patient in the treatment group.

Laparotomy was performed in all patients in the 'resected' group and in 28 of the 'inoperable' group (14 control and 14 treated). In the remainder, diagnosis was made endoscopically and spread was determined by liver scan and biopsy. There was a surgical preference for carrying out a polya-type of partial gastrectomy, with seven total gastrectomies (six control, one treated) and six oesophago-gastrectomies (four controls, two treated).

DRUG REGIME

Therapy was started after sutures were removed and at least 14 days after a major surgical resection or seven days after an exploratory laparotomy. It was not instituted within 10 days of an infection but always started within three months of diagnosis.

Patients were randomised into groups 24 hours before treatment was started and received one of two schedules of treatment, which were known to the treating physicians.

The control group received analgesics and other supportive treatment only, whereas the treatment group received an in-patient initiation course of 5-fluorouracil, methotrexate, vincristine, and cyclophosphamide over five days as shown in Table 3. All drugs were given intravenously as bolus injections followed by 5 ml of normal saline.

Maintenance therapy consisting of 5-fluorouracil (10 mg/kg) and mitomycin-C (100 μg/kg) was given daily for five consecutive days. This was started four weeks after the end of the initiation course and repeated at six-weekly intervals until death, withdrawal, or two years of treatment had been completed.

ASSESSMENT

The duration of symptoms preceding diagnosis, the extent of tumour found at laparotomy, including the presence of lymph nodes, liver metastases, and

Table 2 *Findings in 39 patients in 'resected' group*

		Control	Treatment	Total
Total		20	19	39
Males		14	11	25
Females		6	8	14
Mean age (range) (yr)		62·5 (35–75)	62·6 (43–75)	
Length of history (m)	<6/12	16	13	29
	>6/12	4	6	10
Liver metastases	Present	4	1	5
	Absent	16	18	34
Lymph	Involved	17	17	34
	Not involved	3	2	5
Distant metastases		0	1	1

Table 3 *Drug regime used for initiation course*

Day	*Cyclophosphamide (mg)*	*5-Fluorouracil (mg)*	*Vincristine (mg)*	*Methotrexate (mg)*
1	300	500	–	20
2	—	500	1	—
3	—	500	–	—
4	—	500	–	20
5	300 (4·5 mg/kg)	500 (7·5 mg/kg)	1 (0·02 mg/kg)	— (0·3 mg/kg)

Figures in parentheses denote dosage if patient's weight falls outside 60–80 kg range.

distant metastases, were noted (Tables 1 and 2).

Regular clinical assessments before operation or treatment and at five-weekly intervals thereafter were made using a standard protocol. The following parameters were noted and scored 0–4 depending on severity: pain, nausea, vomiting, stool frequency, weight, hair loss, and analgesic requirement. Well-being was recorded using a patient assessment score and the Karnofsky scale (Karnofsky, 1961). Blood was taken for estimation of haemoglobin, full cell count, ESR, urea, bilirubin, alkaline phosphatase, alanine and aspartate amino transferases, and gamma glutamyl transferase. Liver scans, barium meals, and endoscopy were performed as indicated.

Results

By the end of three years 76 patients had been entered into the trial, 37 had 'inoperable' and 39 had 'resected' gastric adenocarcinoma. Seven of the 76 patients were withdrawn but only two because of toxicity effects—one with marrow depression and one with renal failure. Of the remaining four, one patient declined further treatment and three were lost to follow-up by moving out of the area.

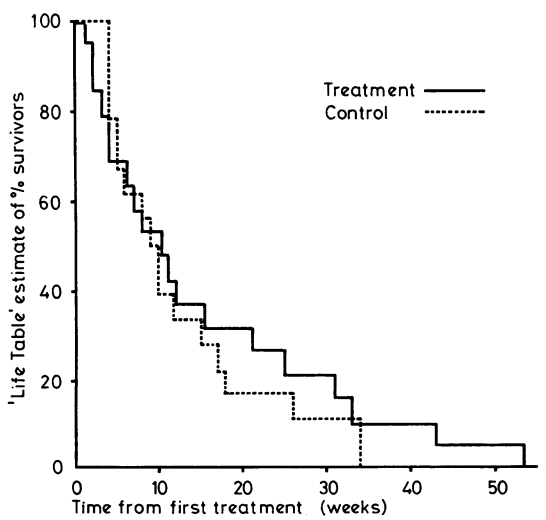

Fig. 1 *Survival graph for patients in the 'inoperable' group.*

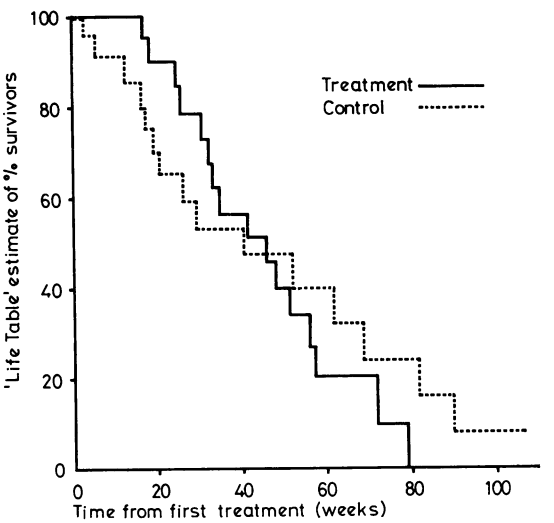

Fig. 2 *Survival graph for patients in the 'resected' group.*

Survival in the treated and control patients was compared using the logrank test recommended by the Medical Research Council's Leukaemia Steering Committee (Peto *et al.*, 1977). Post-operative assessment of survival in the 'inoperable' group showed no significant difference between treated and control patients ($P=0·67$, Fig. 1). The median survival times for the treated and control groups were 9·5 and 9·0 weeks respectively, with an associated 95% confidence interval for the median of four to 21 weeks and five to 15 weeks.

In the 'resected' group there was no difference in the overall survival between the treated and control patients ($P=0·67$, Fig. 2) but up to 20 weeks there was a suggestion that the probability of survival in the treated patients was higher ($P=0·06$). The median survival times (95% confidence intervals in parentheses) were 40 weeks (31 to 55 weeks) for the treated patients and 37 weeks (19 to 66 weeks) for the control patients.

Table 4 *Assessment of pain, nausea, vomiting, and diarrhoea in patients in 'resected' group*

	Pain		*Nausea*		*Vomiting*		*Diarrhoea*	
	T	*C*	*T*	*C*	*T*	*C*	*T*	*C*
No. patients in group	19	20	19	20	19	20	19	20
No. patients ever experiencing symptoms (% in parentheses)	13 (68)	12 (60)	16 (84)	7 (35)	11 (58)	8 (40)	10 (53)	8 (40)
No. of observations	106	84	106	84	106	84	106	84
Mean symptom score/visit	0·54	0·45	0·65	0·15	0·25	0·17	0·29	0·19

T: treatment group.
C: control group.

Non-parametric statistical analysis of the clinical, biochemical, and haematological parameters assessed at different time intervals in the 'resected' groups showed only a difference in nausea symptoms and the ESR readings in the treated and control patients. The ESR readings were significantly increased in the treated group. Table 4 gives additional information on assessment of pain, nausea, vomiting, and diarrhoea, with treated patients showing a significantly higher score for nausea. The mean symptom score per visit compensates for the fact that treated patients had more visits than the controls.

Regular monitoring of the effects of chemotherapy on the blood cell count, showed that no patient had a white cell count below $2x10^9/l$ ($2x10^3/mm^3$) and only one treated patient in the 'resected' group had less that $40x10^9/l$ platelets ($40\,000/mm^3$).

Discussion

The object of a chemotherapy programme must be to prolong survival but this should not be achieved at the expense of intolerable toxic effects or a decrease in quality of life.

Our results in the 'inoperable' group confirm the poor prognosis in unresectable tumours when compared with five-year survival of 60% if early localised lesions are diagnosed, Haas and Schottenfeld (1978), and *Lancet* Editorial (1976).

In the 'resected' group, the chemotherapy regime appeared to be having an effect up to 20 weeks, but after that time the death rate in the treated and control patients was approximately the same. Although these patients were well-matched, in this trial no other attempt has been made to stratify groups, particularly in relation to more accurate tumour staging (Imanaga and Nakazato, 1977; Nakajima *et al.*, 1978) and histological grade (Brookes *et al.*, 1965; Hawley *et al.*, 1970; Ohman and Wetterfors, 1970). We feel that a more detailed study is now indicated to modify and extend the therapeutic regime in order to see if there are any criteria, either of spread or histology, that may make one group more responsive than others to this regime. In this respect we have also been encouraged by the finding of prolonged survival in pancreatic carcinoma patients treated with an identical protocol (Mallinson *et al.*, 1976).

No patient received therapy for longer than two years and, with the therapeutic regime used, only two patients had unacceptable toxicity. One patient with renal failure is still alive after two years and there is no detectable evidence of recurrence of tumour and no deterioration of renal failure once treatment stopped.

The regular follow-up of patients has enabled us to chart changes in the quality of life and to plan terminal care. Only nausea was more frequently recorded in the treatment group, although this was short-lived and manageable. We believe that the quality of life was not impaired in the treated group: overall pain was not significantly reduced, but a few individuals did show a striking reduction in analgesic requirements while on treatment.

Gastric cancer is a common disease for which survival has not improved in the last 20 years. Although earlier diagnosis and complete resection are ideals to be aimed at, the short duration of symptoms before diagnosis in both the 'resected' and 'inoperable' groups, and the impracticability of extensive screening make these ideals unattainable. If any advance is to be made in the treatment of gastric cancer, it must be in the combination of surgery with chemotherapy. Only by carefully controlled clinical trials will any new advances be made towards more effective treatment.

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