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Original Paper

Epirubicin, Cisplatin and Infusional 5-Fluorouracil (5-FU) (ECF) in Hepatobiliary Tumours

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Hepatobiliary tumours are rare, often present late and have a poor prognosis, with no current effective systemic therapy available. This study aimed to evaluate the activity and toxicity of epirubicin, cisplatin and continuous infusional 5-fluorouracil (5-FU) (ECF) in patients with these tumours. From March 1991 to November 1993, 25 patients with advanced biliary tumours and 7 with hepatoma were treated with epirubicin 50 mg/m^2 and cisplatin 60 mg/m^2 intravenously (i.v.) day 1, each given every 21 days and 5-FU 200 mg/m^2/day given as a continuous 24 h i.v. infusion throughout the treatment course. 8 of the 20 (40%) evaluable patients with biliary tumours responded. Median duration of response was 10 months. 2 of the 7 (29%) patients with hepatoma responded. The regimen was well tolerated with minimal haematological and non-haematological toxicity. This novel regimen is active in advanced hepatobiliary tumours.

Key words: hepatobiliary tumours, chemotherapy, ECF
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INTRODUCTION

CARCINOMAS OF the biliary system are rare malignancies accounting for approximately 4–5% of all gastrointestinal (GI) cancer in Europe and the U.S.A. Patients with these tumours often present late and hence curative surgical options are limited and survival rates poor. Chemotherapy has been used to treat patients with advanced disease, 5-fluorouracil (5-FU) being the commonest single agent used, with response rates of approximately 10–20% [1]. A number of small trials of combination regimens has been reported with response rates varying from 8 to 31% [2, 3], although small patient numbers have made conclusions about the effectiveness of chemotherapy difficult.

Worldwide, hepatoma is the commonest fatal cancer, but like biliary cancer, it is relatively uncommon in Europe and North America, and often presents with disease too far advanced for curative surgery to be considered. A large number of anticancer drugs have undergone clinical trials in advanced hepatoma, of which the most active is doxorubicin. Even with this agent, the response rate is less than 20% [4, 5], with the addition of other agents adding little further benefit [6–8].

New combination chemotherapy regimens have been developed, which have been shown to be active in other upper GI tumours, particularly gastric cancer. We have previously reported a 71% response rate with ECF (epirubicin, cisplatin, infusional 5-FU) in patients with advanced gastro-oesophageal cancer [9]. Continuous infusion 5-FU has been shown to produce higher response rates compared with bolus 5-FU in colorectal cancer [10], but has not yet been reported in hepatobiliary tumours. Cisplatin has potential synergy with 5-FU [11], and is reported as having some single-agent activity in hepatoma [12], while the anthracyclines are active in both tumour types. In this paper, we report our experience with ECF in one of the largest reported series of patients with biliary disease, as well as a small series of patients with advanced hepatoma.

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PATIENTS AND METHODS

Patient characteristics

25 patients with advanced biliary cancer and 7 patients with advanced hepatoma were entered into this study between March 1991 and November 1993. All patients had either inoperable disease, residual disease postsurgery or recurrent disease following surgery. Inclusion criteria were as follows: histologically confirmed adenocarcinoma of the ampulla of vater, gall bladder or intra/extra hepatic bile ducts, or hepatocellular carcinoma; glomular filtration rate (GFR) >40 ml per min; and WHO performance status 0–3.

Patients' characteristics are outlined in Table 1. 8 patients with biliary tumours and 3 patients with hepatomas had undergone previous surgery, with 1 (Table 2, patient 21) having positive resection margins postsurgery. One patient (patient 1) had previously been treated with chemotherapy alone (high dose

Table 1. Patients' characteristics

	Biliary tract	Hepatoma
No. of patients	25	7
No. evaluable for response	20	7
Sex		
Male	15	4
Female	10	3
Age (years)		
Median	58	55
Range	26–75	24–68
WHO performance status		
Median	1	1
Range	0–2	0–2
Subtype		
Ampulla of vater	4	
Gall bladder	9	
Cholangiocarcinoma	12	
Previous treatment		
Surgery	8	3
Chemotherapy	1	
Chemotherapy/radiotherapy	1	

Table 2. Tumour response

	CR	PR	SD	PD	NE	Total
Biliary	—	8 (40%)	5 (25%)	7 (35%)	5	25
Hepatoma	—	2 (29%)	2 (29%)	3 (43%)	—	7

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable.

melphalan followed by autologous bone marrow transplantation (ABMT)) while another (patient 14) had received previous combined chemotherapy and radiotherapy.

Treatment regimen

All patients received the following regimen: epirubicin 50 mg/m^2 intravenously (i.v.) day 1 and cisplatin 60 mg/m^2 i.v. day 1, each given every 21 days, and 5-FU given as a continuous i.v. 24 h infusion at 200 mg/m^2 per day throughout the treatment course. All chemotherapy was given via an ambulatory infumed pump (Neurotechnics) and a double lumen indwelling catheter (Quinton, U.S.A.) placed in the subclavian vein via a subcutaneous tunnel under local anaesthetic [13]. Prophylactic low dose warfarin (1 mg/day) was given, to reduce the risk of venous thrombosis associated with indwelling central venous catheters [14]. Patients were instructed in the use of the pump by specialist nurses, and changed their 5-FU infusion bags once weekly at home. Appropriate pre- and post-treatment i.v. hydration was given with cisplatin. In the vast majority of cases, patients received their treatment in our outpatient day unit.

Dose adjustment criteria for cisplatin were based on the GFR, which was estimated using [^{51}Cr]EDTA clearance. If GFR was $\geq$ 60 ml/min, full dose cisplatin was given; if GFR was 40–59 ml/min then the mg dose of cisplatin equalled the GFR value in ml/min. If the GFR was < 40 ml/min, no cisplatin was given.

If symptoms and signs of cardiac disease were present, a multigated cardiac scan was performed. If the left ventricular ejection fraction (LVEF) was <50%, epirubicin was not given. If serum bilirubin was between 15 and 30 mmol/l, epirubicin was given at 50% dose reduction; if bilirubin was >30 mmol/l, the drug was omitted. If patients developed palmar plantar erythema on the continuous infusion 5-FU, pyridoxine was administered initially, but if this toxicity did not improve, 5-FU was discontinued for 1 week and then re-introduced with a 50 mg/m^2 dose reduction. If mucositis or diarrhoea developed, treatment was stopped until these symptoms resolved, followed by recommencement of treatment with a 50 mg/m^2 dose reduction (if toxicity was grade 3 or 4, 100 mg/m^2 dose reduction was used).

If the white cell count was $<2.0 \times 10^9$/l or platelets were $<100 \times 10^9$/l, day 22 treatment was delayed for 1 week or until myelosuppression had resolved. Two episodes of treatment delay or an episode of neutropenic sepsis required a 25% dose reduction of epirubicin.

Assessment of response and toxicity

All patients had pretreatment peripheral full blood count, plasma electrolytes, urea and creatinine, liver function tests, [^{51}Cr]EDTA, chest X-ray and abdominal computed tomography (CT) scan. A full blood count and biochemistry tests were carried out before each treatment cycle and repeat CT scans were performed after three and six cycles. Patients were assessed prior to each treatment for objective response and toxicity, according to standard WHO criteria [15]. All CT scans were assessed by a consultant radiologist. Complete response (CR) was defined as the disappearance of all known disease for at least 4 weeks. Partial response (PR) was defined as a greater than or equal to 50% decrease in the sum of the products of the tumour's longest dimension and its widest perpendicular measurement for at least 4 weeks, without the appearance of new lesions or progression of any one lesion. Stable disease (SD) was defined as a less than 50% decrease or less than 25% increase in the size of the measurable disease, without the appearance of new lesions. Progressive disease (PD) was defined as a >25% increase in one or more of the measurable lesions or the appearance of new lesions. Palmar plantar erythema was graded according to WHO skin toxicity criteria.

Statistical analysis

Response, duration and survival were calculated from the date of first treatment using the standard life table method of Kaplan and Meier [16].

RESULTS

25 patients with biliary tract tumours and 7 patients with hepatoma were entered into the study. All hepatoma patients were evaluable for response. 5 patients with biliary tumours were not evaluable for response—4 had no evidence of measurable disease and 1 patient (patient 25) developed superior vena cava (SVC) thrombosis midway through the first treatment cycle and received no further chemotherapy. All patients were included in survival analysis.

Objective response and survival

Biliary tumours. 8 of 20 evaluable patients (40%; 95% confidence interval (CI) 19–64) with biliary tumours achieved an objective response. The median duration of response was 10 months (range 5–22). 4 patients responded in the liver (Table 3: patients 1, 2, 3, 5), 2 in the lung (patients 6, 7) and 2 in local lymph nodes (patients 7 and 8). 7 patients progressed on

Table 3. Biliary tract—individual patient characteristics and results of treatment

No.	Age/sex	WHO PS	Subtype	Previous treatment	ECF (no.)	Response	Duration response (months)	Further treatment	Survival (months)
Evaluable for response									
1	35/M	1	AV	Resection/chemo*	8	PR	12	ECF × 2 (relapse)	15
2	67/F	1	AV	—	10	PR	11	—	11
3	63/M	0	AV	—	5	PR	4	—	5
4	64/M	1	GB	Resection	6	PR	8	—	9
5	56/F	2	GB	Resection	6	PR	5	—	9
6	69/M	2	GB	—	7	PR	22	—	24
7	61/M	0	Chol	—	7	PR	9	ECF × 3 (relapse)	12
8	55/M	1	Chol	—	5	PR	11	Resection residual disease ECF × 3	13
9	58/F	0	GB	Resection	6	SD			11+
10	58/M	1	GB	—	6	SD		Resection residual disease 5-FU/carbo (relapse)	29+
11	45/M	0	Chol	—	6	SD		Resection residual disease 5-FU/carbo (relapse)	12
12	61/F	1	Chol	—	3	SD			7
13	65/M	2	Chol	—	5	SD			5
14	52/M	1	AV	Resection/chemo†	3	PD		ABMT (carbo/etop)	6
15	68/F	2	GB	—	3	PD			5
16	60/F	1	GB	—	3	PD			8
17	26/M	2	Chol	—	1	PD			3
18	42/F	1	Chol	—	3	PD			4
19	59/M	1	Chol	Resection	1	PD			3
20	52/M	2	Chol	—	3	PD			4
Not evaluable for response									
21	41/F	1	Chol	Resection	6				9
22	54/M	1	Chol	—	8				14
23	47/F	1	Chol	—	5				7+
24	75/M	2	GB	—	1				2
25	64/F	2	GB	—	1				5

AV, Ampulla of vater; GB, gall bladder carcinoma; Chol, cholangiocarcinoma; ECF, epirubicin–cisplatin–infusional 5-FU; PS, performance status; M, male; F, female; PR, partial response; SD, stable disease; PD, progressive disease; carbo, carboplatin; ABMT, autologous bone marrow transplantation; etop, etoposide.
*ABMT (melphalan); †5-fluorouracil/radiotherapy; +Still alive.

chemotherapy, 2 during the first treatment course. A summary of tumour response is shown in Table 2. Of the 4 patients with no measurable disease, 1 is alive and well at 7 months, while 3 died at 2, 14 and 9 months. 3 of 4 patients with ampulla of vater tumours responded, 3 of 7 with gall bladder cancer responded, while only 2 of 9 patients with cholangiocarcinoma responded. These differences were not significant either in terms of tumour response ($P = 0.2$) or survival ($P = 0.73$). 2 patients, both with gall bladder cancer, survived for 24 months or longer. There were no notable differences in terms of treatment response ($P = 0.5$) or survival ($P = 0.9$) between patients with performance status 0–1 and those with performance status 2. Median survival was 11 months and overall survival is shown in Figure 1.

Hepatomas. 2 of 7 patients (29%) had a PR, and both are alive and well with continuing response at 5 and 17 months. 3 patients progressed on treatment. Median survival in this group of patients was 8 months. Individual patients' responses to treatment are shown in Table 4.

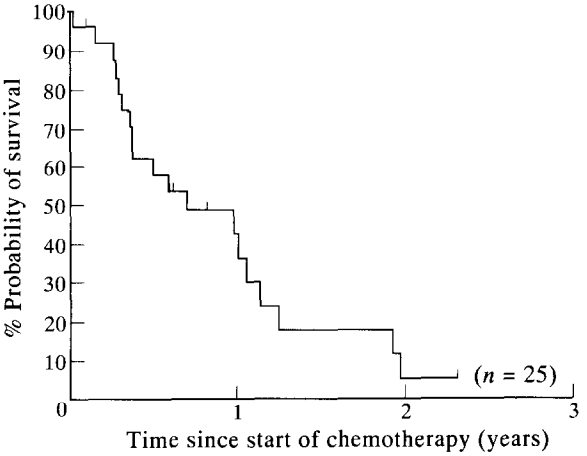

Figure 1. Overall survival—biliary patients.

Toxicity

Overall, this regimen was well tolerated. Haematological toxicity was minimal, with only 5 patients (16%) developing WHO grade 3/4 neutropenia and 6 patients (19%) grade 3/4 thrombocytopenia. 4 patients developed significant neutropenic infection. All responded well to treatment, and there were no toxic neutropenic deaths. Severe emesis was not a major problem, with only 2 patients (6%) developing grade 3/4 toxicity. 10 patients (31%) developed significant alopecia. Stomatitis and

Table 4. Hepatomas—individual patient characteristics and results of treatment

No.	Age/sex	WHO PS	Disease status	Previous treatment	ECF (no. of cycles)	Response	Duration response (months)	Further treatment (at relapse)	Survival (months)
1	27/F	1	Recurrent disease (fibrolamellar)	L hepatectomy 1988	8	PR	17	—	17+
2	31/F	0	Recurrent disease (fibrolamellar)	R hepatectomy 1989	6	PR	5	—	5+
3	55/M	1	Unresectable	—	4	SD	—	Epirubicin × 5	8
4	68/M	1	Unresectable	—	8	SD	—	—	17
5	58/M	1	Unresectable	—	4	PD	—	—	4
6	24/F	0	Recurrent disease	L hepatectomy 1992	3	PD	—	Epirubicin × 3	12
7	68/M	2	Unresectable	—	1	PD	—	—	2

+Still alive.
L, left; R, right. For abbreviations see legend to Table 3.

diarrhoea, although common problems were only severe (grade 3/4) in 1 (3%) and 4 (13%) patients, respectively. Other significant side-effects, including neuropathy or nephropathy, were rare. Specific treatment toxicities are outlined in Table 5.

One hundred and sixty-two cycles of ECF were administered to 32 patients overall. The median number of treatment cycles given was five (range 1–10). Ninety-one per cent of the intended dose of epirubicin was administered per course, 93% of cisplatin and 92% of 5-FU. Fifty-six per cent of patients required a dose reduction at some stage of the treatment, the majority of which were 5-FU related.

6 patients (19%) had Hickman line complications, requiring removal of the line. These included 3 patients with significant line infections and 3 patients with thrombosis of the SCV or axillary vein. In 1 further patient the line spontaneously fell out. No patient required cessation of therapy because of Hickman line complications.

DISCUSSION

For the majority of patients that present with advanced biliary tract carcinoma or hepatoma, there is currently no standard effective treatment. The aim of this study was to test the efficacy and tolerability of a new regimen that we have previously found to be very active in gastro-oesophageal cancer [9].

Table 5. WHO toxicity—worst grade for all courses

	Grade						
	0	1	2	3	4	% 1–2	% 3–4
Haematological							
Anaemia	25	7	—	—	—	22	—
Leucopenia	14	6	7	1	4	41	16
Thrombocytopenia	23	1	2	2	4	9	19
Non-haematological							
Infection	17	8	3	3	1	34	13
Emesis	6	11	13	2	—	75	6
Mucositis	21	4	6	1	—	31	3
Diarrhoea	15	6	7	4	—	41	13
Alopecia	6	7	9	10	—	50	31
Palmar plantar	18	9	5	—	—	44	—
Neuropathy	29	3	—	—	—	9	—
Nephrotoxicity	25	7	—	—	—	22	—

Single-agent systemic chemotherapy in biliary tract tumours has principally involved bolus 5-FU, with response rates in the region of 10–20% [1]. The addition of alkylating agents or nitrosoureas has been tested in the past, but found to have little benefit over 5-FU alone [1]. The addition of doxorubicin to combination regimens appears to have improved response rates, with Hall and associates reporting three out of seven responses for the combination of ftorafur, doxorubicin and BCNU (carmustine) [2]. The FAM (5-FU, doxorubicin, mitomycin C) regimen, originally developed for gastric cancer, has also been shown to be active in this disease, with a reported response rate of 31% [3]. Small patient numbers and the fact that a number of reports have combined results for hepatoma and biliary cancer have made it difficult to establish the true response rate for this tumour type. This, in addition to the fact that overall survival remains poor, has meant a continued search for new and active regimens.

Our current study is the second largest single series of biliary tract tumours treated with a uniform chemotherapeutic regimen, and an objective response rate of 40% represents significant activity. A possible reason for the improved activity of this regimen over previously reported regimens may be the use of continuous infusion 5-FU, allowing a much greater dose intensity without accompanying increased toxicity compared with bolus administration. Although suggesting an improved response rate, the number of patients studied along with the variable natural history of the different tumour subgroups does not allow definitive statements about the effect of ECF on survival, although the median survival of 11 months is in keeping with other reports.

Whilst biliary tract tumours are certainly chemosensitive, the experience with chemotherapy of advanced hepatoma has been less impressive. Doxorubicin has been considered the agent of choice, although at least one randomised study has failed to show a benefit for doxorubicin versus no treatment [4]. Numerous combination regimens have been tried systemically. Bezwoda and associates reported a response rate of 44% in 36 patients with advanced hepatoma [6], however, other doxorubicin-containing regimens have failed to support this, suggesting little benefit over doxorubicin alone [7, 8]. This report suggests that ECF has activity in hepatocellular carcinoma, but the small number of patients precludes any further conclusion in terms of comparison with other reported regimens.

ECF was extremely well tolerated by the patients. Major haematological toxicity was minimal and, although 16% of patients developed grade 3/4 myelosuppression, the 4 patients who developed neutropenic fever were easily managed with no toxic neutropenic deaths. Significant emesis or alopecia were minimal, an important consideration in a regimen primarily concerned with palliation.

In patients with locally advanced unresectable biliary tract tumours, radiotherapy alone has not been shown to improve survival. Anecdotal reports have been published of an apparent improvement in survival with combined modality therapy, which up until now has principally involved the use of 5-FU as a radiation sensitiser [17, 18]. These results are preliminary but encouraging and this approach requires further study.

ECF is a new combination chemotherapy regimen which is active and well tolerated in hepatobiliary tumours. We plan to continue to evaluate it in the setting of advanced metastatic disease, looking in detail at the effect on quality of life and symptom response, as well as assessing it in combination with radiotherapy in patients with locally advanced disease.

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