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Phase II Study of Epirubicin in advanced Adenocarcinoma of the Pancreas

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For the EORTC Gastrointestinal Group

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Abstract—*The EORTC Gastrointestinal Group has conducted a phase II trial in* 41 *patients with locally advanced or metastatic adenocarcinoma of the pancreas with epirubicin* 90 mg/m^2 *intravenously every* 4 weeks, *with dose escalation if possible. Seven patients were not evaluable for response. In* 34 *evaluable patients there were two complete and six partial responses (response rate* 24%). *Nine patients had stable disease for at least* 2 months, *including one patient with a minor response. Median time to progression for responders was* 7 months, *for all patients* 3 months. *Median survival for responders was* 9 months, *for all patients* 5 months. *It is concluded that epirubicin is an active drug in pancreatic cancer.*

INTRODUCTION

PROGNOSIS in advanced adenocarcinoma of the pancreas is dismal [1]. Only few single agents have activity in this disease, 5-fluorouracil being the most extensively evaluated drug [1]. Epirubicin (4′-epi-adriamycin, 4′-epi-doxorubicin) is a new anthracycline antibiotic. It differs from doxorubicin by the epimerization of the OH group in position 4′ of the amino sugar moiety and was synthesized in an effort to find agents with a superior therapeutic index to the parent compound doxorubicin. Pharmacokinetics of the two drugs are different and the acute and chronic toxicity of epirubicin is less than of doxorubicin in equimolar doses [2]. Two preliminary communications suggested that epirubicin might have activity in this disease [3, 4]. This prompted the EORTC Gastrointestinal Group to conduct a phase II study with this anthracycline derivative in patients with measurable locally advanced or metastatic adenocarcinoma of the pancreas.

MATERIALS AND METHODS

Patients could enter the study if they fulfilled the following eligibility criteria: histologically proven adenocarcinoma of the pancreas, age $\leqslant$ 70 yr, performance status 0–2 (ZUBROD), no previous treatment with irradiation or cytostatic drugs, bilirubin $\leqslant 30\ \mu$mol/l and measurable disease. Computed tomography (CT) and ultrasound were accepted as methods to measure lesions provided the minimal diameter of the measurable lesion was at least 5 cm. Epirubicin was given in a dose of 90 mg/m^2 intravenously (i.v.) day 1 and repeated every 4 weeks with dose escalation (10 mg/m^2) in the next cycles in the absence of major toxicity. Response was evaluated after every 2 cycles.

Definition of response was according to WHO criteria, i.e. partial remission (PR) was defined as at least 50% reduction in the sum of the products of the two largest perpendicular diameters of the measurable lesions; stable disease (SD) as unchanged lesions (<50% decrease or <25% increase) for at least 2 months. All scans of responding patients were seen and agreed upon by at least three independent investigators. Patients had to receive a minimum of two cycles of chemotherapy to be evaluable for response.

RESULTS

From July 1982 until December 1983 41 eligible patients from 11 institutions in five countries were entered. The patient characteristics are shown in Table 1. Out of these 41 patients seven were not evaluable for response due to refusal after one cycle (one patient), early death due to tumour

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Table 1. Patient characteristics

Registered patients	46
Eligible patients	41
Not evaluable	7
Evaluable	34
Median age (yr)	55
Male/female	22/12
Median Zubrod scale	1
Median weight loss (percentage of previous body weight)	5-10
Locally advanced	11
Locally advanced + metastatic	20
Metastatic (primary excised)	3

Table 2. Results

No. of evaluable patients	34	
CR	2/34	24%
PR	6/34	
SD	9	
PD	17	
Median duration of response (months)	7	
Median survival responders (months)	9	
Median survival all patients (months)	5	

progression (four patients) or early death due to other reasons (two patients; one cerebrovascular accident, one peritonitis). The median number of courses was four (range 2-11) and the mean dose per course 96 mg/m² (range 90-120 mg/m²). Twenty-two patients had dose escalation. In 34 evaluable patients eight remissions were observed, two complete and six partial (Table 2). In seven out of these eight patients a dose escalation had been given. Nine patients had SD, including one patient with a minor response, i.e. a clear regression of tumour without fulfilling the PR criteria. Median duration of remission was 7 months (range 2-17), median survival for the responders 9 months (range 2-18+) and median survival for all patients 5 months.

The two CRs were documented by CT-scanning and the duration of remission was 8 and 17 months. One patient had locally advanced disease plus liver metastases, the other only locally advanced disease. Their survival was 9 and 18+ months respectively. Four responses were observed at the first evaluation i.e. after the second cycle. There were four patients who developed a remission after at least four cycles and in three of them the dose had been escalated up to 110 mg/m². The PRs were noted at the level of the primary [1], primary and liver [3], liver metastases only [1] and palpable abdominal mass (one patient). Figure 1 shows the survival curves of all patients including and excluding the early deaths.

Toxicity of epirubicin was relatively mild. Major toxicity consisted of hair loss, median grade 2 (WHO gradations) and nausea/vomiting, median grade 1. The median white cell count on day 14 was 2.7 × 10^9/l (range 0.6-11.5). Thrombocytopenia was not observed. There were no toxic deaths.

DISCUSSION

The development of chemotherapy in pancreatic carcinoma has proceeded relatively slowly. One of the problems is the fact that response to chemotherapy can often only be measured by techniques such as ultrasound and CT-scanning. These techniques can only be accepted as reliable parameters if they are interpreted by experienced investigators.

Only few single agents have been adequately tested in more than 20 patients and only three

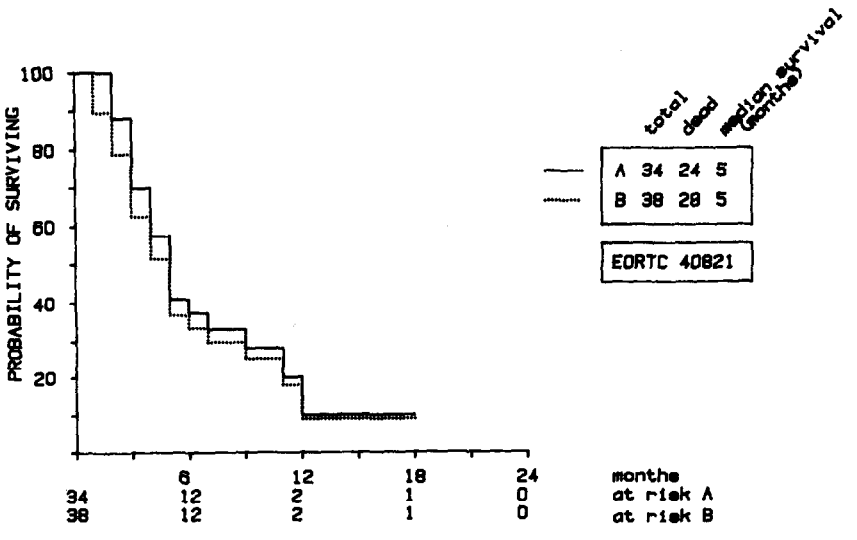

Fig. 1. Survival curves (Kaplan Meier) for all eligible patients including (. . . .) and excluding (——) early deaths.

Table 3. Activity of single agents in pancreatic cancer

Drug	Responders/ No. of patients	Response rate (%)	Reference
5-FU	60/212	28 (20)	[1, 5]
Mitomycin C	12/44	27	[1, 6]
Streptozotocin	8/22	36	[1, 6]
Ifosfamide	4/21	19	[7]
Adriamycin	2/15	13	[8]
Methyl CCNU	3/34	9	[9]
Vindesine	1/15		[10]
Methotrexate	1/25		[8]
Actinomycin C	1/28		[8]
BCNU	0/20		[11]

drugs appear to have a response rate over 20% (Table 3). 5-Fluorouracil (F) is the most extensively evaluated drug; in recent studies a response rate of about 20% has been reported [1, 5]. Response rates for mitomycin-C (M) and streptozotocin (S) as shown in Table 3 are also compilations from collected series [1, 6]. Adriamycin (A) has been tested by the Gastro Intestinal Tumour Study Group (GITSG) and yielded a response in 2/15 (13%) patients [8]. Despite the relatively few active drugs there has been continued interest in combination chemotherapy. Table 4 gives an overview of phase II pilot studies in advanced pancreatic carcinoma. FAM and SMF are the most employed regimens. The response rate is about 30%, the median survival of responders about 10 months and the overall median survival 6 months. Approximately 10% of patients seems to survive over 1 yr. A randomized study comparing FAM versus SMF in 112 patients, however, showed only 9 and 4% response rates and median overall survival of 28 and 18 weeks respectively [20]. In another randomized study of 116 patients with measurable disease conducted by the South West Oncology Group (SWOG), SMF was compared with MF. The response rates were 23 and 8% respectively but median survivals were similar, 18 vs 17 weeks [21]. Comparison of all of these studies should be done cautiously. Studies conducted by different institutions or by different cooperative groups may produce vastly different response rates. Part of this variability is explained by patient selection difference and part by a stricter definition of measurable disease.

This EORTC-study has shown that epirubicin is an active drug in locally advanced and metastatic adenocarcinoma of the pancreas. Response rate in evaluable patients was 24% (confidence intervals 11-41%). Including the early deaths due to tumour progression, the response rate (8/38) was 22% (confidence intervals 10-37%). These results are comparable to those of combination chemotherapy. The suggested higher activity of epirubicin as opposed to doxorubicin in this disease may be dose-related, this higher dose of epirubicin being possible by its attenuated toxicity. Another possibility is that the drug may have different biologic properties despite its chemical similarity with doxorubicin. It is obvious, however, that the prognosis in metastatic pancreatic carcinoma remains dismal and a continuous effort must be made to identify new active regimens. The promising activity of epirubicin as reported in this trial, recently confirmed by others [22], should encourage such further studies.

Table 4. Combination chemotherapy in advanced pancreatic carcinoma (excludes comparative studies—see text)

Regimen	No. of patients	No. of responders	Median survival responders (months)	Median survival all patients (months)	Survivors >1 yr	Reference
SMF	23	10	10	6	4	[12]
SMF	22	7	9	6		[13]
FAM	27	10	12	6	4	[14]
FAM	15	6	13+	4	1	[15]
FAM-S	25	12	10	7	7	[16]
FAP	15	3	10+			[17]
HEXA-FAM	30	5		4		[18]
HEXA-FM	21	2		10		[19]
Total	178	55 (31%)	10	6	16 (9%)	

S = streptozotocin; M = mitomycin; F = 5-fluorouracil; A = adriamycin; P = *cis*-platinum; HEXA = hexamethylmelamine.

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