Pergamon

European Journal of Cancer Vol. 32A, No. 8, pp. 1310–1313, 1996

Printed in Great Britain
0959-8049/96 $15.00+0.00

PII: S0959-8049(96)00070-6

Original Paper

Results of a Phase II Trial of Epirubicin and Cisplatin (EP) Before and After Irradiation and 5-Fluorouracil in Locally Advanced Pancreatic Cancer: An EORTC GITCCG Study

D.J.Th. Wagener,[1] W.J. Hoogenraad,[1] Ph. Rougier,[2] A. Lusinchi,[2] B.G. Taal,[3] C.H.N. Veenhof,[4] A. de Graeff,[5] T. Conroy,[6] D. Curran,[7] T. Sahmoud[7] and J. Wils[8]

[1]University Hospital Nijmegen, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands; [2]Institut G. Roussy, Villejuif, France; [3]Antoni van Leeuwenhoek Hospital, Amsterdam; [4]Academic Medical Center, Amsterdam; [5]Academic Hospital, Utrecht, The Netherlands; [6]Centre Alexis Vautrin, Nancy, France; [7]EORTC Data Center, Brussels, Belgium; and [8]St. Laurentius Hospital, Roermond, The Netherlands

The objective of the present study was to define the role of chemotherapy, in the form of the EP regimen, consisting of epirubicin (E) and cisplatin (P) in addition to irradiation in combination with 5-fluorouracil (5-FU) for treatment of pancreatic cancer. 53 eligible patients with histologically or cytologically proven locally advanced pancreatic cancer were treated with three cycles of E 60 mg/m² (if this dose was well tolerated then the dose of E was increased by 10 mg/m² in the next cycle; 80 mg/m² was the maximum dose for the following cycles) and P 100 mg/m² once every 3 weeks, followed after 4 weeks by a split course of irradiation of 40 Gy with 5-FU 500 mg/m² on each of the first 3 days of each 20 Gy treatment segment. This was followed by another three cycles of EP in patients who achieved stable disease (SD) or a better response after the first three cycles. The treatment given with standard anti-emetics was moderately tolerated. The chemotherapy related toxicity consisted mainly of myelosuppression and the chemoradiotherapy related toxicity of gastrointestinal side-effects. However, due to the long duration of treatment which made the whole treatment difficult to endure, only 18/53 (34%) actually completed the full treatment regimen. Responses were evaluated after the first three cycles and 4 weeks after the completion of the treatment by serial CT-scans using standard criteria. The results in 53 evaluable patients after the first three cycles of EP were as follows: 1 patient achieved a clinical complete response (CR), 7 a partial response (PR) (CR + PR: 15%; 95% confidence interval (CI): 11–33%), 36 patients (68%) had stable disease (SD) and 6 patients progressive disease (PD). There was 1 early PD, 1 toxic death and 1 patient could not be evaluated. The response at the end of the treatment was 3 CR, 11 PR (CR + PR: 14/53 (26%); 95% CI: 15–40%), 30 SD and 6 PD. The median time to progression was 8.9 months and the median duration of response 13.1 months. The median survival of all treated patients was 10.8 months (range 7 days to 41.5 months), of responders 15.1 months and, of the patients with SD 10.3 months. These results are comparable to other combined modality regimens reported in the literature for locally advanced disease. The addition of the systemic treatment with E and P offers no additional advantage to combined modality treatment alone.

Key words: locally advanced pancreatic cancer, combined modality treatment
Eur J Cancer, Vol. 32A, No. 8, pp. 1310–1313, 1996

INTRODUCTION

THE INCIDENCE of adenocarcinoma of the pancreas has steadily increased over the past four decades [1]. Despite tremendous efforts in early diagnosis and therapy the prognosis is still dismal. The percentage of surgically resectable patients is less than 20%, and of those resected the median survival is only 9–15 months [2, 3] while 5-year survival rates are less than 5% [4, 5].

Approximately 40% of patients with pancreatic cancer present with locally advanced disease [6]. This stage has been defined as unresectable disease due to regional lymph node involvement and/or encasement of major blood vessels, but

Correspondence to D.J.Th. Wagener.
Received 27 Mar. 1995; revised 1 Jan. 1996; accepted 9 Feb. 1996.

without evidence of hepatic or other distant metastases. To be staged as locally advanced, it should be possible to encompass the tumour in a moderately sized upper gastrointestinal radiation target volume. Currently accepted management involves the use of combined modality treatment with 5-fluorouracil (5-FU) and radiation therapy [7].

Chemotherapy is poorly active [8], but previous studies from our EORTC group have reported an objective significant response after epirubicin treatment [9] and cisplatin administration [10].

The objective of the present study was to define the role of chemotherapy, in the form of the EP regimen, consisting of epirubicin (E) and cisplatin (P) in addition to irradiation in combination with 5-FU for treatment of pancreatic cancer.

PATIENTS AND METHODS

Eligibility

All patients entered into this trial had histologically or cytologically proven ductal adenocarcinoma of the pancreas. Inclusion criteria included the following: inoperable disease due to ingrowth in surrounding tissue or positive regional lymph nodes; no distant metastases on chest X-ray—anterior–posterior and lateral—and on the CT-scan of the whole abdomen; age less than 71 years; WHO performance status ≤ 2; kidney and liver function tests normal; WBC $\geq 4 \times 10^9$/l, platelet count $\geq 100 \times 10^9$/l; all regional disease encompassed within a 400 cm^2 radiation therapy field. Informed consent was required. Criteria for exclusion were: prior chemotherapy or radiotherapy, active infection, brain or leptomeningeal disease, concomitant other malignant disease and overt cardiac disease.

Statistical considerations

The first endpoint analysed was response to treatment. Survival and side-effects were also described.

The sample size calculation was based on the two-stage Gehan's design aiming to include 9 patients and then including additional patients according to the number of responses observed in the first stage. This guarantees that the probability of an active treatment (real response rate $\geq 30\%$) exhibiting no responses in the first 9 patients (that is, false negative result) is 0.05 and allows the effectiveness of the treatment regimen to be estimated with a standard error of 10% [11].

Survival curves and time to progression curves were estimated using the Kaplan–Meier technique [12].

Treatment

The chemotherapy was given according to the following schedule: E 60 mg/m^2 i.v. on day 1. If this dose was well tolerated, then the dose of E was increased by 10 mg/m^2 in the following cycles to 80 mg/m^2 as the maximum dose. P 100 mg/m^2 diluted in 1 litre normal saline was administered over a 4-h period with adequate pre- and posthydration. The cycle was repeated every 21 days. The drug dose was modified for subsequent courses according to the degree of haematological toxicity (Table 1).

If the treatment had to be postponed for more than 4 weeks, the response to treatment was evaluated and the patient went off study. The dose of E was reduced by 50% in the presence of a bilirubin level of 35–50 mmol/l; no epirubicin was given if this level reached >50 mmol/l.

After three cycles of EP, the patients were given irradiation therapy as described by the Gastrointestinal Tumor Study Group [7] consisting of 40 Gy (split course) in combination with 5-FU (500 mg/m^2) given as a bolus injection immediately prior to radiotherapy on days 1–3 of the two irradiation periods of 2 weeks each, with an interval of 2 weeks. After the irradiation, another three cycles of EP were given if after three cycles stable disease (SD) or a better response was achieved.

Table 1. Dose attenuation schedule for bone marrow depression

Leucocytes (× 10^9/l)	Thrombocytes (× 10^9/l)	Epirubicin	Cisplatin
> 4	> 100	100%	100%
3–4	75–100	75%	75%
< 3	< 75	Postpone 1 week	

The patients were evaluated for response after three cycles of chemotherapy and 4 weeks after six cycles. The response was assessed by computerised tomography (CT). The response was defined according to WHO guidelines for non-measurable disease [13]. A complete response (CR) was therefore defined as the complete disappearance of all known disease. A partial response (PR) was defined as an estimated decrease in tumour size of $\geq 50\%$, and no change (NC) was defined as no significant change. The latter included SD, an estimated decrease in tumour size $\leq 50\%$, and lesions with an estimated size increase of $<25\%$. Disease progression (PD) was defined as the appearance of a new lesion not previously identified or an estimated increase of $\geq 25\%$ in the size of existent lesions. A confirmation after 4 weeks was required in case of CR or PR. The duration of response and of survival were measured from the start of chemotherapy. Toxicity was assessed using a 0–4 grading system according to the WHO [13]. The RTOG/EORTC Late Radiation Morbidity Scoring scheme was also used for the small/large intestine, liver, kidney, spinal cord and skin.

RESULTS

Between October 1987 and January 1992, 61 patients with locally advanced disease were registered into the trial. Six patients did not fulfil the inclusion criteria: no measurable lesions for 2 patients, 1 had an inadequate histology, 1 liver metastases, 1 had ascites and 1 also had breast cancer and was treated with CMF. 2 other patients, although eligible, were excluded from the analysis because they experienced digestive haemorrhage before the treatment could start. Consequently, the results are based on the 53 eligible patients for whom the treatment started. The patient characteristics are given in Table 2. All 53 patients had histological confirmation of adenocarcinoma of the pancreas.

Of the 53 eligible patients, 49 received the required initial three cycles of chemotherapy. Of these 49 patients, 8 had progression and therefore were not given any further treatment and 1 patient refused further treatment due to persistent nausea and vomiting. In addition to the remaining 40 patients, 1 more patient, who received only two cycles of chemotherapy, received radiotherapy because he was considered unfit for further chemotherapy. Out of these 41 patients who received radiotherapy, 37 completed the radiotherapy split course while the other 4 patients received only the first part. 2 patients could not tolerate any more treatment, 1 suffered a digestive haemorrhage and jaundice and the other had progressive disease. Among the 37 patients who completed the split

Table 2. Patient characteristics

	$n = 53$
Age (years)	
Median (range)	59 (37–70)
Sex	
Male	34
Female	19
Weight loss (%)	
None	8
⩽ 10	15
> 10	27
Unknown	3
WHO performance status	
0	22
1	29
2	2
Prior surgery	
None	22
Palliative	31

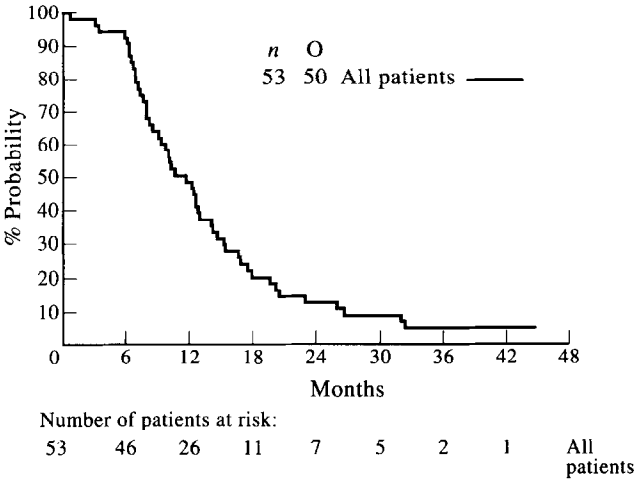

Figure 1. Duration of survival.

course, 24 patients received further chemotherapy and 13 patients did not receive any more chemotherapy: 8 patients had progression, 3 refused further treatment, and treatment was stopped for 2 patients due to toxicity. Treatment was stopped for 1 patient due to excessive toxicity after the fourth cycle of chemotherapy. 5 more patients had only five cycles: 2 due to toxicity, 1 refused further treatment, 1 had a very poor digestive tolerance and 1 was lost to follow-up after the fifth cycle. 18 patients (34%) completed the additional three cycles of chemotherapy.

The response after the first three cycles of chemotherapy was 1 CR, 7 PR (CR + PR: 8/53, 15%; 95% CI: 7–28%), 36 SD and 6 PD (Table 3).

The response at the end of the treatment was 3 CR, 11 PR, making an overall response rate of 26% (14/53, 95% CI: 15–40%). 30 patients achieved SD. 7 patients had PD, of whom 1 patient had early progression. 1 patient had an early death due to septic shock during leucopenic period and 1 patient could not be evaluated after treatment.

At the time of the analysis, 3 patients were alive; 50 patients had died, 46 due to progressive disease, 2 due to toxicity of the chemotherapy, 1 because of pulmonary infection, 1 due to cerebral insufficiency.

The median duration of survival of all treated patients was 10.8 months (range 7 days to 41.5 months. The 1-year survival was 49% (95% CI: 35–63%) (Figure 1).

The median survival of responding patients was 15.1 and of patients with SD 10.3 months. The median time to progression was 8.9 months and the median duration of response 13.1 months.

Toxicity and side-effects of chemotherapy and irradiation are shown in Tables 4 and 5, respectively.

The chemotherapy was in general well tolerated. The grade 3 toxicity for nausea and vomiting is due to the WHO scoring

Table 4. Chemotherapy side-effects ($n = 53$) (worst grade)

Side-effect	0	1	2	3	4	Pre-existing	Unknown
WBC	50	2	0	1	0	0	0
Granulocytes	43	0	5	0	0	0	5
Platelets	26	13	6	2	6	0	0
Nausea/vomiting	1	5	15	30	2	0	0
Diarrhoea	26	12	12	1	0	2	0
Oral	45	5	3	0	0	0	0
Liver	46	4	1	0	1	0	1
Renal	40	8	3	1	0	0	1
Hair	9	2	10	30	0	1	1
Infection	38	8	3	2	1	0	1
Peripheral neuropathy	46	4	2	0	0	0	1

Table 3. Response to treatment

	After 3 cycles	Overall
Complete response	1	3
Partial response	7	11
Stable disease	36	30
Progression	6	6
Early progression	1	1
Early death due to septic shock during leucopenic period	1	1
No evaluation during or after the treatment (two cycles)	1	1

Table 5. Side-effects due to chemo-irradiation (n = 41)

Side-effect	0	1	2	3	4	Unknown
WBC	39	0	0	0	0	2
Granulocytes	26	0	0	0	0	15
Platelets	26	6	5	2	0	2
Gastro-intestinal	8	19	8	5	1	0
Small/large intestine	24	9	6	0	0	2
Liver	38	0	1	1	0	1
Kidney	39	1	0	0	0	1
Spinal cord	41	0	0	0	0	0
Skin	41	0	0	0	0	0

system which indicates a 3 if anti-emetics are given prophylactically. In fact, most patients received anti-emetics by which the treatment was tolerable. The split course irradiation in combination with 5-FU was also generally well tolerated.

DISCUSSION

Treatment of locally advanced pancreatic cancer is at best palliative. The best approach seems to be a combination of systemic treatment with irradiation [8]. However, only one randomised trial has proven this [7]. According to data from the literature, a median survival between 8.4 and 14 months can be expected with the combined approach, whereas the median survival for untreated patients with locally advanced disease is between 3–5 months [8].

The aim of this study was to investigate the role of the addition of systemic treatment in the form of E and P to the known local treatment consisting of irradiation in combination with 5-fluorouracil. The treatment was moderately tolerated. The chemotherapy-related toxicity consisted mainly of myelosuppression and the chemoradiotherapy-related toxicity of gastrointestinal side-effects. However, although according to WHO criteria the toxicity was mild, the long duration of the treatment period makes the complete treatment difficult to endure.

The results obtained in this study (median survival 10.8 months) are not superior to the data obtained with the combined modality treatment published in the literature [7]. Therefore, we conclude that the addition of the systemic treatment with E and P seems to offer no additional advantage and cannot be recommended, although simpler regimens of chemotherapy followed by irradiation (± chemotherapy) might be worth assessing, particularly because of the potential advantage of identifying the initial chemotherapy responders.

To place the results of this trial in proper perspective, it should be noted that this was a multicentre study and that there was no upper limit to the size of the tumour in patients treated in this study. Patients with tumours as great as 11 cm in diameter were included in the trial. It is likely that patients with such large tumours have distant metastases.

The combined modality approach is only worthwhile for localised disease. Therefore, the staging procedure in locally advanced disease should include a laparoscopic evaluation. Nearly half the patients with presumed resectable localised disease appear to have small but visible abdominal metastases during laparoscopy [14, 15]. In the non-resectable cases, this is probably even more.

From an experimental and theoretical point of view, it is of importance for future trials not to interrupt the cytostatic treatment period.

Another reason not to divide the treatment period is that only about half the patients could be treated according to the planned treatment schedule and could receive chemotherapy after the irradiation. For most patients, the whole schedule is too difficult to endure and in addition, because most of the responses were documented after the first three cycles, it remains questionable whether the postirradiation courses of chemotherapy are of any use.

To improve the results of treatment of pancreatic cancer, it is of great importance to have more effective chemotherapy schedules. New drugs or better combination treatments are urgently needed.

An important question which should also be answered in the near future is: what is the best chemo-irradiation regimen? From the radiobiological point of view, the split course irradiation is now considered outdated, but so far no irradiation schedule has been demonstrated to be superior.

1. Silverberg E. *NCI 3rd National Cancer Survey.* Department of Epidemiology and Statistics, American Cancer Society, New York, 1978.
2. Leadbetter A, Foster RS, Haines CR. Carcinoma of the pancreas. Results of the Vermont Tumor Registry. *Am J Surg* 1975, **129**, 356–360.
3. Cornelly MM, Dawson RJ, Michelassi F. Survival in 1001 patients with carcinoma of the pancreas. *Ann Surg* 1987, **206**, 366–373.
4. Morrow M, Hilaris B, Brennan MF. Comparison of conventional surgical resection, radioactive implantation and bypass procedures for exocrine carcinoma of the pancreas. *Ann Surg* 1984, **199**, 1–5.
5. Gudjonsson B. Cancer of the pancreas, 50 years of surgery. *Cancer* 1987, **60**, 2284–2303.
6. Brennan MF, Kinsella TJ, Casper ES. Cancer of the pancreas. In DeVita VT, Hellman S, Rosenberg SA, eds. *Cancer, Principles and Practice of Oncology.* Lippincott, Philadelphia, 1993, 852.
7. Moertel CG, Frytak S, Hahn RG, *et al.* Therapy of locally unresectable pancreatic carcinoma: a randomized comparison of high dose (6000 rads) radiation alone, moderate dose radiation (4000 rads + 5 fluorouracil) and high dose radiation + 5 fluorouracil (Gastrointestinal Tumor Study Group). *Cancer* 1981, **48**, 1705–1710.
8. Wagener DJTh, de Mulder PHM, Wils JA. Multimodality treatment of locally advanced pancreatic cancer. *Ann Oncol* 1994, **5**, S81–S86.
9. Wils J, Bleiberg H, Blijham G, *et al.* Phase II study of epirubicin in advanced adenocarcinoma of the pancreas. *Eur J Cancer* 1985, **21**, 191–194.
10. Wils JA, Kok T, Wagener DJTh, *et al.* Activity of cisplatin in adenocarcinoma of the pancreas. *Eur J Cancer* 1993, **29A**, 203–204.
11. Gehan EA. The determination of the number of patients required in a preliminary and follow up trial of a new chemotherapy agent. *J Chron Dis* 1961, **13**, 346–353.
12. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Ass* 1958, **53**, 457–481.
13. WHO. *Handbook for Reporting Results of Cancer Treatment.* (Offset publication 48) WHO, Geneva, 1979.
14. Warzhaw AL, Tepper JE, Shipley WU. Laparoscopy in the staging and planning of therapy for pancreatic cancer. *Am J Surg* 1986, **151**, 76–80.
15. Cuschieri A. Laparoscopy for pancreatic cancer. Does it benefit the patient? *Eur J Surg Oncol* 1988, **14**, 41–44.