PERGAMON

European Journal of Cancer 38 (2002) 648–653

European Journal of Cancer

www.ejconline.com

Results of a randomised phase II study of cisplatin plus 5-fluorouracil versus cisplatin plus 5-fluorouracil with α-interferon in metastatic pancreatic cancer: an EORTC gastrointestinal tract cancer group trial

D.J.T. Wagener[a,*], J.A. Wils[b], T.C. Kok[c], A. Planting[d], M.L. Couvreur[e], B. Baron[e]

[a]*UMC Nijmegen, PO Box 9101, 6500 HB Nijmegen, The Netherlands*
[b]*Laurentius Hospital, Roermond, The Netherlands*
[c]*University Hospital Rotterdam Dijkzigt, Rotterdam, The Netherlands*
[d]*University Hospital Rotterdam Daniel, Rotterdam, The Netherlands*
[e]*EORTC Data Center, Brussels, Belgium*

Received 30 July 2001; accepted 8 August 2001

Abstract

A randomised phase II study of 5-fluorouracil (5-FU) plus cisplatin (CDDP) with or without α-interferon 2b was performed in patients with pancreatic cancer with measurable metastatic disease outside the pancreas. The treatment in arm A consisted of cisplatin (100 mg/m^2) on day 1, followed by a continuous infusion of 5-FU 1000 mg/m^2 for 4 days and in arm B the same treatment was given plus α-interferon 2b in a dose of 3 million Units/day subcutaneously (s.c.) from day 1 for 5 days. 36 patients were entered in the trial, 18 in each arm. In arm B only 15 patients were eligible. No responses were observed in the 5-FU/CDDP arm and only 2 partial responses were achieved in the interferon-arm, lasting 27 and 32 weeks, respectively. Both treatment arms showed considerable toxicity. It has to be concluded that both treatment regimens have little activity and cannot be recommended.

Keywords: Pancreatic cancer; Phase II study; Cisplatin plus 5-fluorouracil; Cisplatin plus 5-fluorouracil plus α-interferon

1. Introduction

Patients with advanced pancreatic cancer have an extremely poor prognosis. The median survival of patients with locally advanced disease is 5 months, or 2 months for those with distant metastases [1]. Chemotherapy represents the principal palliative treatment of choice in inoperable pancreatic cancer with response rates of less than 15% when stringent criteria are used and a median survival of 4 months (range 2–8.3 months) [2]. 5-Fluorouracil (5-FU) is the most commonly used drug with a reported wide range of activity between 0 and 28% using a variety of doses and schedules [3]. The combination of 5-FU with other active drugs is not more effective than 5-FU alone and no standard therapy can be recommended at present [4].

In 1987, the European Organization of Research and Treatment of Cancer Gastrointestinal Tract Cancer (EORTC GITC) Group initiated a randomised phase II trial of chemotherapy with cisplatin versus ifosfamide in advanced pancreatic cancer. It appeared that ifosfamide was not active (response rate 0% in 26 patients [5]), whereas cisplatin showed a response rate of 21% in 33 patients [6].

Synergistic activity of cisplatin and 5-FU has been reported in several tumours. A 26% response rate was seen in 38 patients with advanced pancreatic cancer with a median response duration of 9.7 months [7].

Studies in experimental human cancers have suggested that interferons may enhance the response to cytotoxic drugs [8,9]. A non-randomised study of the combination of cisplatin with α-interferon in patients with advanced non-small cell lung cancer showed an overall partial response rate of 30% in 60 evaluable patients [10]. In addition, in colon carcinoma very promising results were found with the combination of

* Corresponding author. Tel.: +31-24-361-5215; fax: +31-24-354-0788.
E-mail address: d.wagener@onco.azn.nl (D.J.T. Wagener).

0959-8049/02/$ - see front matter
PII: S0959-8049(01)00319-7

α-interferon with 5-FU [11–15]. No potentiation of haematological, renal or neurological toxicity was seen. Interferons may interact with 5-FU in a greater than additive fashion to produce cytotoxicity [16]. It has been suggested that the interaction is based on the enhancement of DNA-directed actions such as thymidylate synthetase inhibition or DNA incorporation [17]. Besides this possible synergistic effect of interferon, there is some evidence suggesting an active inhibition of cell growth by interferon, probably by interfering with processes following (epidermal) growth factor receptor activation. Epidermal growth factor can promote pancreatic carcinogenesis in animals and also the growth of human pancreatic cancer cells *in vitro* [18,19]. Moreover, the pancreas itself is one of the richest sources in the body of mRNA for the epidermal growth factor [20], and human pancreatic cancer cells overexpress the gene for epidermal growth factor receptor as much as 100-fold [21].

These observations provided the rationale for the randomised phase II study comparing cisplatin plus 5-FU alone and cisplatin plus 5-FU α-interferon in patients with measurable metastatic pancreatic cancer.

2. Patients and methods

2.1. Patient selection

All patients entered in this trial had histologically- or cytologically-proven adenocarcinoma of the pancreas with measurable disease outside the pancreas. Further eligibility criteria were: World Health Organization (WHO) performance score 0–2, age less than 75 years, no previous chemotherapy and immunotherapy, no previous radiotherapy to sites of measurable disease, no overt cardiac disease and no central nervous system involvement. Adequate organ function with creatinine inferior to 130 μmol/l, bilirubin $\leqslant 40$ μmol/l, white blood count $>4.0\times10^9$/l; platelets $>100\times10^9$/l were required.

Informed consent was obtained from all patients after the nature of the study had been fully explained and the protocol was approved by the institutional review board.

3. Treatment and methods

The patients were randomised between arm A: cisplatin (CDDP) plus 5-FU and arm B: CDDP plus 5-FU with α-interferon. The treatment consisted of CDDP (100 mg/m^2) on day 1, with conventional hydration to prevent nephrotoxicity, followed immediately after the cisplatin by a continuous infusion of 5-FU in a dose of 1000 mg/m^2/24 h from day 1 for 4 days and in arm B cisplatin and 5-FU plus α-interferon 2b (Intron-A) in a dose of 3 million Units/day subcutaneously (s.c.), from day 1 (starting 2 h before the start of cisplatin) for 5 days. The courses were repeated every 4 weeks.

The main endpoints of this study were the response rate and the duration of response. Secondary endpoints included toxicity, time to progression and survival time.

Tumour response was determined by computed tomography scan and/or ultrasound scan. Patients were evaluated for toxicity after each cycle, and for response every two cycles. The WHO scores for response were used. If a response or no change was documented, treatment was continued until progression. The duration of response and time to treatment failure was calculated from the randomisation date to progression and survival was calculated from the registration to death. The National Cancer Institute (NCI) Canada common toxicity criteria were used. Before treatment all patients were admitted to hospital for the insertion of a venous central catheter (port a cath or similar device).

3.1. Statistical considerations

For each arm separately the Simon one sample two stage testing procedure was used to decide if both drugs should be further investigated ($\alpha=0.10$ and $\beta=0.05$). At the first step, if the response rates were not at least 10% in both arms, the drugs would be rejected from further testing. At the second step, if the results of the trial were compatible with a response rate of 35% then the drugs would be further investigated in a phase III study. 30 patients were to be included for the first step (15 in each arm). Depending on the number of responses, >2 in each arm, an additional 18 patients were to be included for the second step (9 in each arm). The final conclusion was that a regimen with a number of responses greater than or equal to 5 should be further investigated.

All analyses were performed twice, once on the eligible patients only and once on all randomised patients. The safety analyses were restricted to patients who started their treatment. Survival curves (Overall Survival and Time to Progression) were estimated using the Kaplan–Meier technique [22].

4. Results

Between November 1994 and May 1996, 36 patients (18 in each arm) were randomised at the EORTC Data Center by 8 institutions (Fig. 1). The purpose of randomisation in the phase II of the study was a simultaneous screening for an eventual phase III, therefore no comparisons can be drawn based on the results of this phase II. There were 18 patients randomised in both treatment arms, however, 3 patients randomised in the interferon arm were ineligible. 2 patients had no lesions suitable as

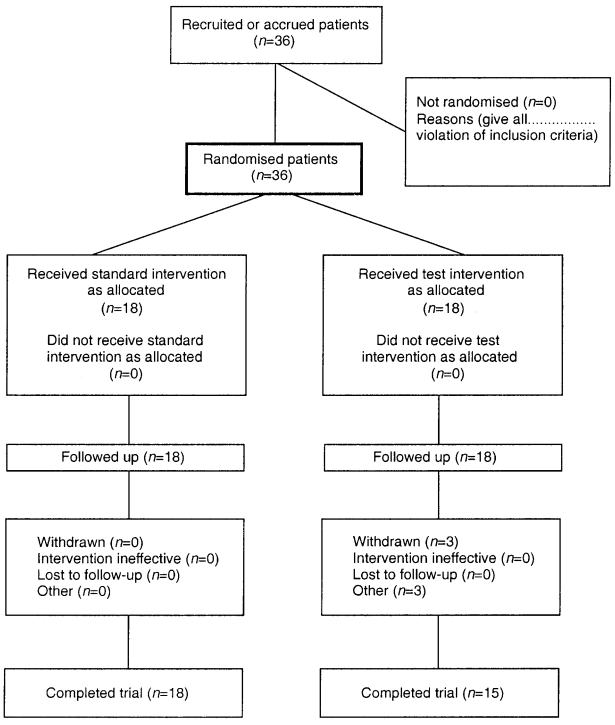

Fig. 1. Flow chart of the progress of patients through the trial. (adapted from Ref. [25].

a target lesion for evaluation of response outside of the pancreas and the third had no proven adenocarcinoma. Therefore, the total number of eligible patients in the study was 33.

Patient characteristics at randomisation are presented in Table 1 for eligible patients.

As shown the main metastatic site was the liver.

The number of cycles of treatment administered varied between 1 and 6 with a median of 2 in the 5-FU-CDDP arm and a median of 3 in the 5-FU-CDDP-interferon arm.

4.1. Toxicity

The toxicity data of eligible patients are reported in Table 2. Treatment-related toxicity resulted in hospitalisation in 8 patients in the 5-FU-CDDP arm and in 7 patients in the 5-FU-CDDP-interferon-arm. In the 5-FU-CDDP arm, there was one toxic death. The patient had hypomagnesaemia, neurocortical toxicity grade 3, cardiac dysrhythmia grade 4, diarrhoea grade 4 and thrombocytopenia grade 4.

The reasons for treatment discontinuation are provided in Table 3.

4.2. Response

The best overall responses reported for the eligible patients are described in Table 4. There were no responses in the 5-FU-CDDP arm and two partial responses in the interferon arm. The duration of these responses was 27 and 32 weeks, respectively. In the 5-FU-CDDP arm, among the 18 eligible patients, 5 were not assessable for the response evaluation. Follow-up measurements were not performed for 4 patients and the fifth patient had a target lesion which became non-evaluable.

Overall survival curves and time to progression curves are given in Figs. 2 and 3 for the eligible patients.

In the 5-FU-CDDP arm, the median survival time was 6.5 months and the median time to progression 5 months, in the 5-FU-CDDP-interferon arm, the median

Table 1
Patient characteristics at randomisation (eligible patients)

	5-FU-CDDP arm ($n=18$)	Interferon arm ($n=15$)
Patient data		
Age (years)		
Median (range)	58 (33–69)	58 (46–68)
Sex		
Male	11	10
Female	7	5
Weight loss relative to usual weight (%)		
None	2	3
< 5	3	2
5–10	3	1
11–20	8	7
>20	1	2
Unknown	1	0
Performance status		
0	3	3
1	14	10
2	1	2
Location of primary tumour		
Head and/or peri-ampullary region	11	8
Body	2	2
Tail	4	5
Not assessable	1	0
Prior surgery		
None	12	11
Curative	1	0
Palliative	5	4
Sites involved		
Number of target lesions		
1	3	0
2	5	6
3	8	8
4	1	1
6	1	0
Sites involved		
Pancreas	15	12
Liver	14	13
Lung	2	2
Regional nodes	3	1

5-Fu, 5-fluorouracid; CDDP, cisplatin.

Table 2
Toxicity grade 3-4 according to the NCI Canada- CTC (eligible patients)

	5-FU-CDDP arm ($n=18$)	5-FU-CDDP-Interferon arm ($n=15$)
Haematological toxicity		
WBCs		
3	2	0
4	1	1
Granulocytes		
3	3	0
4	2	1
Unknown	3	0
Platelets		
3	0	2
4	1	2
Haemoglobin		
3	1	1
Serum bilirubin		
3	4	5
Stomatitis/mucositis		
3	2	1
4	1	0
Nausea		
3	5	3
4	1	0
Vomiting		
3	6	1
4	2	1
Diarrhea		
3	1	0
4	1	1
Fever in absence of infection		
3	1	0
Alopecia		
3	1	2
Infection		
3	1	0
Neuro-sensory		
3	0	2
Neuro-cerebellar		
3	0	1
Neuro-cortical		
	1	0

NCI, National Cnacer Institute; CTC, Common Toxicity Criteria; WBC, Whole Blood Cells.

survival time was 5 months and the median time to progression 3 months.

5. Discussion

In the 5-FU-CDDP arm, no response was achieved (confidence interval (CI) of 0–19%). Nine patients had stable disease and 4 patients progressed. Grade 4 toxicities occurred in white blood cells (WBC), granulocytes, platelets, stomatitis mucositis, nausea, vomiting and diarrhoea. The median survival time was 6.5 months and the median time to progression was 5 months. In the 5-FU-CDDP-interferon arm, 2 patients of the 15 eligible patients had a partial response, 7 had stable disease, 3 progressed and 3 patients had an early death, 2 due to malignant disease and the third one probably from progression, but evaluation could not be performed due to a bad psychological condition. The median survival time was 5 months and, the median time to progression was 3 months.

Grade 4 toxicities were the same in the α-interferon arm as in the 5-FU-CDDP-arm, but grade 3 consciousness toxicity was also observed.

According to the design of the trial, the interferon arm should have continued to accrue patients, but the second response was reported very late after the trial was closed to patiënt entry and because of the poor results it has not been reopened.

Table 3
Reasons for treatment discontinuation (eligible patients)

Reason	5FU-CDDP arm ($n=18$)	Interferon + 5 FU-CDDP arm ($n=15$)
Normal completion of protocol treatment	4	3
Progression (including death due to progression)	6	10
Toxicity (including death due to toxicity)	4	1
Patient's refusal (not due to toxicity)	3	1
Deterioration of patient condition	1	0

5-FU, 5-fluorouracid; CDDP, cisplatin.

Table 4
Best overall response (eligible patients)

	5FU-CDDP arm ($n=18$)	Interferon + 5FU-CDDP arm ($n=15$)
Partial response (CI)	0 (0–19%)	2 (2–41%)
Stable disease	9	7
Progression of disease	4	3
After 1 cycle	3	1
After 2 cycles	1	1
After 3 cycles	0	1
Early death	0	3
Malignant disease		2
Other[a]		1
Not assessable	5	0

Cl, confidence interval; 5-FU, 5-fluorouracil; CDDP, cisplatin.
[a] Died at home probably from progression.

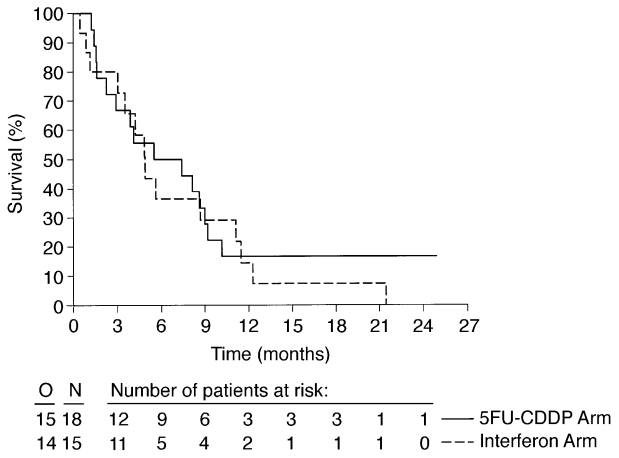

Fig. 2. Overall survival curves (eligible patients). 5-FU, 5-fluorouracid CDDP, cisplatin; O, Observed; N, Number.

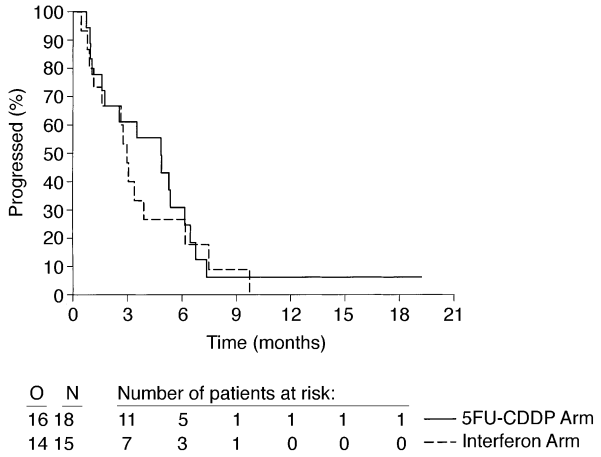

Fig. 3. Time to progression (eligible patients). 5-Fu, 5-fluorouracid; CDDP, cisplatin; O, observed; N, Number.

The disappointing outcome of this study is in-line with the results obtained with 5-FU and α-interferon in colon carcinoma [23]. In a randomised trial of 5-FU alone (750 mg/m^2/day by continuous infusion for 5 days followed by 750 mg/m^2 weekly) versus 5-FU plus interferon (10 MU s.c. three times weekly) in patients with measurable metastatic colorectal cancer, a 30% objective tumour response occurred in patients receiving 5-FU alone and 19% for those receiving 5-FU plus interferon. In addition, an adjuvant study in rectal cancer with 5-FU, leucovorin and radiation therapy with or without interferon showed no significant improvement of the results following the addition of interferon [24].

It has to be concluded that both treatment schedules have little activity and cannot be recommended.

Acknowledgements

The study was supported by a grant from Schering-Plough Research Institute, Kenilworth, USA.

References

1. Wagener Th DJ, Mulder PHM, de Wils JA. Multimodality treatment of locally advanced pancreatic cancer. *Ann Oncol* 1994, **5**, 81–86.
2. Schnall SF, McDonald JS. Chemotherapy of adenoca of the pancreas. *Semin Oncol* 1996, **23**, 220–228.
3. Evans DB, Abbruzzese JL, Rich TA Cancer of the pancreas. In De Vita VT Jr, Hellman S, Rosenberg SA, eds. *Cancer, Principles and Practice of Oncology*, 5th Ed. Lippincott-Raven, Philadelphia, 1997, 1054–1087.
4. Lionetto R, Pugliese V, Bruzzi P, Rosso R. No standard treatment is available for advanced pancreatic cancer. *Eur J Cancer* 1995, **31A**, 882 –887.
5. Wils JA, Kok TC, Wagener Th DJ, Francois E, Selleslags J, Deuz N. Phase II trial with ifosfamide in pancreatic cancer. *Eur J Cancer* 1993, **29A**, 290.
6. Wils JA, Kok TC, Wagener Th DJ, Selleslags J, Duez N. Activity of cisplatin in adenocarcinoma of the pancreas. *Eur J Cancer* 1993, **29A**, 203–204.
7. Rougier Ph., Zarba J., Ducreux M., Basile M., Cvitkovich S., Droz J.P., Armand J.P. Efficacy of combined 5FU and CDDP in advanced pancreatic adenocarcinoma. Int Conf on Biology and Treatment of Gastro-intestinal Malignancies. *Book of Abstracts*, 70.
8. Carmichael J, Fergusson RJ, Wolf CR, *et al*. Augmentation of cytotoxicity of chemotherapy by human α-interferons in human non-small cell lung cancer xenografts. *Cancer Res* 1986, **46**, 4916–4920.
9. Wadler S, Schwartz EL. Antineoplastic activity of the combination of interferon and cytotoxic agents against experimental and human malignancies: A review. *Cancer Res* 1990, **50**, 3473–3486.
10. Bowman A, Fergusson RJ, Alsan SG, *et al*. Potentiation of cisplatin by α-Interferon in advanced non-small cell lung cancer (NSCLC): A phase II study. *Ann Oncology* 1990, **1**, 351–353.
11. Wadler S, Wiernik PH. Clinical update on the role of fluorouracil and recombinant interferon alfa-2a in the treatment of colorectal carcinoma. *Semin Oncol* 1990, **17**(Suppl 1), 16.
12. Pazdur R, Ajani JA, Patt YZ, *et al*. Phase II study of fluorouracil and recombinant interferon alfa-2a in previously untreated advanced colorectal carcinoma. *J Clin Oncol* 1990, **8**, 2027–2031.
13. Kemeny N, Younes A, Seiter K, *et al*. Interferon alfa-2a and 5-fluorouracil for advanced colorectal carcinoma: assessment of activity and toxicity. *Cancer* 1990, **66**, 2470–2475.
14. Wadler S, Lembersky B, Atkins M, *et al*. Phase II trial of fluorouracil and recombinant interferon alfa-2a in patients with advanced colorectal carcinoma: an Eastern Cooperative Oncology Group study. *J Clin Oncol* 1991, **9**, 1806–1810.
15. Humberman M, McClay E, Atkins M, *et al*. Phase II trial of 5-fluorouracil and recombinant interferon alpha-2a in advanced colorectal cancer. *Proc Am Soc Clin Oncol* 1991, **10**, 153.
16. Chu E, Zinn S, Boarman D, *et al*. Interaction of gamma-Interferon and 5-fluoro-uracil in the H630 human colon carcinoma cell line. *Cancer Res* 1990, **50**, 5834–5840.
17. Wadler S, Schwartz EL, Goldman M, *et al*. Fluoro-uracil and recombinant α-2A-interferon: An active regimen against advanced colorectal carcinoma. *J Clin Oncol* 1989, **7**, 1769–1775.
18. Chester F, Gaissert MA, Ross JA, Malt RA. Pancreatic cancer in the Syrian hamster induced by N-nitroso bis (2-oxypropyl)-amine: carcinogenic effect with epidermal growth factor. *Cancer Res* 1986, **46**, 2954–2970.
19. Malt RA, Chester JF, Gaissert HA, Ross JS. Augmentation of chemically induced pancreatic and bronchial cancers by epidermal growth factor. *Gut* 1987, **28**(Suppl), 249–252.
20. Sporn MB, Roberts AB. Autocrine growth factors and cancer. *Nature* 1985, **313**, 745–747.
21. Korc M, Meltzer P, Trent J. Enhanced expression of epidermal growth factor receptor correlates with alterations of chromosome

7 in human pancreatic cancer cells. *Proc Natl Acad Sci USA* 1986, **83**, 5141–5144.
22. Kaplan EL, Meier P. Nonparametric estimation form incomplete observations. *J Am Statist Ass* 1958, **53**, 457–481.
23. Hill MN, Norman A, Cunningham D, *et al*. Royal Marden Phase III trial of fluorouracil with of without interferon alpha-2b in advanced colorectal cancer. *J Clin Oncol* 1995, **13**, 1297.
24. Gennatas C, Vlahonikolis J, Dardoufas C. Surgical adjuvant therapy of rectal carcinoma: a controlled evaluation of fluorouracil, leucovorin and radiation therapy with and without interferon α-2 b. *ASCO proc* 1999, **18**, 240.
25. Begg C, Cho M, Eastwood S, *et al*. Improving the quality of reporting of randomised controlled trials: the CONSORT statement. *JAMA* 1996, **276**, 637–639.