Eur J Cancer, Vol. 29A, No. 2, pp. 203–204, 1993.
Printed in Great Britain

0964–1947/93 $5.00 + 0.00

Activity of Cisplatin in Adenocarcinoma of the Pancreas

J.A. Wils, T. Kok, D.J.Th. Wagener, J. Selleslags and N. Duez

The activity of cisplatin in metastatic adenocarcinoma of the pancreas was assessed in 33 patients. Cisplatin was administered in a dose of 100 mg/m², every 4 weeks. There were 2 complete responses and 5 partial responses (a response rate of 21%). The median duration of response was 5 months (range, 2+ to 15 months). Cisplatin is a modestly active drug in advanced pancreatic cancer.
Eur J Cancer, Vol. 29A, No. 2, pp. 203–204, 1993.

INTRODUCTION

THUS FAR, chemotherapy has not produced a clear benefit in advanced pancreatic cancer and a continuous search for active agents and/or new treatment approaches is needed. In some phase II trials a benefit for cisplatin-containing combination chemotherapy has been reported [1, 2], but this could not be confirmed in randomised studies [3, 4]. Surprisingly, no trials assessing cisplatin as a single agent have been reported. Therefore, the EORTC Gastrointestinal Tract Group initiated a phase II trial with cisplatin in patients with advanced adenocarcinoma of the pancreas.

PATIENTS AND METHODS

Patients with histologically or cytologically confirmed metastatic pancreatic cancer who were not pretreated were accepted for this study. Additional eligibility criteria included age ≤ 70 years, performance status ≤ 2 and adequate organ functions. Standard WHO response criteria were used. Liver metastases required assessment by computed tomography (CT) scans or ultrasound while for the primary only CT scans were accepted. Response had to be assessed after every two cycles. Toxicity was graded according to standard WHO criteria.

The treatment schedule consisted of cisplatin, 100 mg/m², intravenously every 4 weeks, with adequate pre- and post-hydration. Treatment had to be continued until progression or severe toxicity. For practical reasons and to avoid selection bias as much as possible, a randomised phase II design was chosen and patients were allocated to treatment with cisplatin or with ifosfamide.

RESULTS

A total of 36 patients were entered by nine institutions from The Netherlands, Belgium and France; five institutions entered only 1 patient. The randomised design was discontinued after randomisation of 25 patients, because the ifosfamide arm was closed at that time. A further 11 patients were registered. 33 patients were fully evaluable. The characteristics of these patients are listed in Table 1. Although the study protocol required only patients with metastatic disease, 3 patients with locally advanced disease only were registered and kept in the study. All other patients had metastatic disease. Reasons for non-evaluability were insufficient organ status (1 patient) and treatment never started (2 patients).

There were 2 complete responses and 5 partial responses, while 6 cases had stable disease after two cycles. All other patients progressed after at least one cycle. Cases of early progression and early death for whatever reason (4 cases) were considered failures. The median number of cycles was two, range one to six. 1 complete response was in a patient with locally advanced disease and the other in a patient with liver metastases. Partial responses occurred in 1 patient with locally advanced disease, in 1 patient with lymph node metastases and in 3 patients with liver metastases. The median duration of response was 5 months (range 2+ to 15 months). The duration of the complete responses were 6 and 15 months. The median survival of all evaluable patients was 4 months.

The side-effects were those to be expected and consisted mostly of nausea/vomiting. There was no grade 4 non-haematological toxicity and no severe nephrotoxicity or myelosuppression.

DISCUSSION

In this study 7 responses were observed in 33 evaluable patients with advanced pancreatic cancer (response rate 21%), which is not different from other phase II studies with cisplatin-

Table 1. Patient characteristics (evaluable patients)

Patients	33
Male/female	23/10
Age	
Median	55
Range	27–70
Performance status (WHO)	
0	3
1	23
2	7
Site of metastases	
Locally advanced only	3
Liver	26
Lung	1
Lymph node only	2
Bone	1

Correspondence to J.A. Wils.
J.A. Wils is at the Department of Oncology, Laurentius Hospital, 6043 CV Roermond; T. Kok is at the Department of Oncology, University Hospital Dijkzigt, Rotterdam; D.J.Th. Wagener is at the Department of Oncology, University Hospital Radboud, Nijmegen, The Netherlands; and J. Selleslags and N. Duez are at the EORTC Data Center, Brussels, Belgium, on behalf of the Gastrointestinal (GI) Tract Group of the European Organization for Research and Treatment of Cancer (EORTC).
Revised 21 July 1992; accepted 12 Aug. 1992.

containing combination chemotherapy, which usually yielded response rates of around 20% [1, 2, 5, 6]. Two of the 7 responses in our study, however, were obtained in patients with locally advanced disease who were in fact not eligible. Of 30 patients with metastatic cancer, 5 responded (response rate 17%; 95% confidence intervals 9–39%). Cisplatin, therefore, can be considered a modestly active drug in advanced pancreatic carcinoma and a further search for combinations with other active agents appears reasonable. Continuous infusion (CI) of 5-FU has gained a renewed interest, especially in the treatment of advanced colorectal cancer and is also of potential interest in pancreatic cancer. A phase II study of cisplatin, 100 mg/m^2 every 4 weeks, combined with CI of 5-FU, days 1–5, yielded a 27% response rate in 38 patients [5]. Another study, in which protracted CI of 5-FU was combined with weekly cisplatin, 20 mg/m^2, yielded a 16% response rate [6].

Another possible approach is the combination of active cytotoxic drugs with biological agents such as interferons, because synergism with these agents has been observed *in vitro* and *in vivo* [7, 8]. Therefore, our group is now planning to assess the combination of cisplatin with alpha-interferon.

1. Moertel CG, Rubin J, O'Connell MJ, *et al.* A phase II study of combined 5-fluorouracil, doxorubicin and cisplatin in the treatment of upper gastrointestinal adenocarcinomas. *J Clin Oncol* 1986, **4**, 1053–1057.
2. Dougherty JB, Kelsen D, Kemeny M, *et al.* Advanced pancreatic cancer: A phase I–II trial of cisplatin, high-dose cytarabine, and caffeine. *J Natl Cancer Inst* 1989, **81**, 1735–1737.
3. Cullinan S, Moertel C, Wieand H, *et al.* A phase III evaluation of drug combinations in the therapy of advanced pancreatic cancer. *Proc Am Soc Clin Oncol* 1989, **8**, 124 (abstract).
4. Hudis C, Kelsen D,Dougherty J, *et al.* A randomized trial of streptozotocin (S), mitomycin (M), and 5-fluorouracil (F) (SMF) vs cisplatin (P), ara-c (A), and caffeine (C) (CAC) in advanced pancreatic cancer (PC). *Proc Am Soc Clin Oncol* 1990, **9**, 107 (abstract).
5. Rougier Ph, Zarba J, Ducreux M, *et al.* Efficacy of combined 5-FU and CDDP in advanced pancreatic adenocarcinoma (APC). *Abstr Int Conf on Biol and Treatment of Gastrointest Tract Malign* 1992, Frankfurt, Feb. 4–7, p.70.
6. Rothman H, Cantrell JE, Lokich J, *et al.* Continuous infusion 5-fluorouracil plus weekly cisplatin for pancreatic carcinoma. *Cancer* 1991, **68**, 264–268.
7. Carmichael J, Fergusson RJ, Wolf CR, *et al.* Augmentation of cytotoxicity of chemotherapy by human alpha-interferon in human non-small cell lung cancer xenografts. *Cancer Res* 1986, **45**, 4916–4920.
8. Bowman A, Fergusson RJ, Alson SG, *et al.* Potentiation of cisplatin by alpha-interferon in advanced non-small cell lung cancer (NSCLC): a phase II study. *Ann Oncol* 1990, **1**, 351–353.

Acknowledgements—Other investigators who contributed patients in this study were:
M. Gignoux, CHU, Caen, France; M. Buset, Hopital Erasme and Hopital Brugmann, Brussels, Belgium; M. Fickers, De Wever Hospital, Heerlen, The Netherlands; E. Francois, Centre Antoine Lacassagne, Nice, France; A. de Graeff, Academic Hospital Utrecht, The Netherlands.

Eur J Cancer, Vol. 29A, No. 2, pp. 204–207, 1993.
Printed in Great Britain

0964–1947/93 $5.00 + 0.00

Testing the Possible Non-cross Resistance of Two Equipotent Combination Chemotherapy Regimens Against Small-cell Lung Cancer: A Phase II Study of the EORTC Lung Cancer Cooperative Group

Pieter E. Postmus, Egbert F. Smit, Anne Kirkpatrick and Ted A.W. Splinter

The Goldie–Coldman hypothesis of alternating non-cross resistant combination chemotherapy regimens for small-cell lung cancer has never been adequately evaluated. In previously reported studies non-cross resistance and/or equipotency of the combinations used had not been tested before the phase III study was started. We describe two combination chemotherapy regimens with comparable efficacy against small-cell lung cancer and present a phase II test of their possible non-cross resistance. Patients clinically resistant to cyclophosphamide, doxorubicin and etoposide (CDE), were treated with the second-line regimen consisting of vincristine, ifosfamide, mesna and carboplatin (VIMP) (n = 25). This resulted in 1 complete and 14 partial responses, response rate 60% [95% confidence interval (CI): 38.7–78.9%]. Patients clinically resistant to vincristine, carboplatin (n = 22) or ifosfamide, mesna, carboplatin (n = 21) were treated with CDE, resulting in 6 complete responses and 16 partial responses, response rate 51% (95% CI: 35.5–66.7%). The clinical value of such a degree of non-cross resistance has to be evaluated in a phase III study.
Eur J Cancer, Vol. 29A, No. 2, pp. 204–207, 1993.

INTRODUCTION

SMALL-CELL LUNG CANCER (SCLC) is a chemotherapy-sensitive tumour with response rates of 80–90% in most studies evaluating combination chemotherapy regimens. Despite this initially impressive result, the number of patients with long-term disease-free survival is less than 10%. One of the reasons for this is existence of chemotherapy-resistant cell clones, either present from the start of treatment, or emerging during treatment. Evidence for emerging heterogeneity and resistance can be found in clinical investigations as well as from cell lines and heterotransplanted tumours.

Goldie and Coldman have proposed a simple mathematical model of the probability of the development of resistant cell clones within a tumour [1]. This model assumes that tumours