Eur J Cancer, Vol. 27, No. 11, pp. 1383–1385, 1991.
Printed in Great Britain

0277–5379/91 $3.00 + 0.00
Pergamon Press plc

Randomised Phase II Trial of Carboplatin and Iproplatin in Advanced Urothelial Cancer

R. de Wit, M. Tesselaar, T.C. Kok, C. Seynaeve, C. J. Rodenburg, J. Verweij, P.A. Helle and G. Stoter

47 patients with advanced urothelial cancer and no prior chemotherapy were randomly assigned to therapy with either carboplatin or iproplatin. Both platinum analogues were administered intravenously every 28 days at doses of 400 mg/m² carboplatin and 300 mg/m² iproplatin. None of 14 evaluable patients treated with carboplatin responded. Therefore, this arm was closed and from then on all eligible patients were registered on the iproplatin arm. 5 of 29 evaluable patients treated with iproplatin achieved a partial response (17%) for a median duration of 27 weeks (range 22–37). Iproplatin did not induce renal function disturbance. Gastrointestinal toxicity was mild to moderate. Bone marrow toxicity predominantly consisted of thrombocytopenia and required platelet transfusions in 13% of patients. 2 patients developed hypersensitivity reactions. It is concluded that the bone marrow toxicity and the chance of hypersensitivity render iproplatin an unattractive alternative to cisplatin.
Eur J Cancer, Vol. 27, No. 11, pp. 1383–1385, 1991.

INTRODUCTION

CISPLATIN is the most active single agent for the treatment of advanced urothelial cancer [1, 2]. Combination chemotherapy with cisplatin and methotrexate with or without vinblastine and doxorubicin is superior to single-agent therapy, but also more toxic [2–7]. The dose-limiting side-effect with cisplatin is renal toxicity [8]. Since patients with urothelial cancer often have obstructive uropathy, treatment with cisplatin may be difficult.

Two cisplatin analogues—carboplatin and iproplatin—are less nephrotoxic, neurotoxic and ototoxic [9–11]. The dose-limiting side-effect of these drugs is myelosuppression, predominantly thrombocytopenia [12].

We conducted a randomised phase II study of carboplatin and iproplatin in patients with advanced urothelial cancer to assess the antitumour activity of these drugs and to further define the toxicity of each compound.

PATIENTS AND METHODS

Patients

Eligibility criteria required histologically proven transitional cell carcinoma of the urinary tract, measurable distant metastases or measurable pelvic tumour not amenable to local regional treatment, performance status (WHO scale) 0–2, serum creatinine below 150 μmol/l, white blood cell (WBC) above 3.5×10^9/l and platelets above 100×10^9/l. Patients with prior systemic chemotherapy, irradiated indicator lesions or brain metastases, or of poor medical risk were excluded.

Study design

Patients were randomised to either carboplatin or iproplatin to ensure equal distribution of eligible patients. The carboplatin arm was closed at the time that none of 14 evaluable patients had responded. From then on all eligible patients were registered on the iproplatin arm. Both drugs were administered intravenously in 250 ml normal saline over 60 min, every 4 weeks. The dosage of carboplatin was 400 mg/m² and of iproplatin 300 mg/m² per cycle without hyperhydration. If at scheduled retreatment WBC was below 3.5×10^9/l or platelets below 100×10^9/l, treatment was postponed for a maximum of 2 weeks. If after 2 weeks delay WBC was between 2.0 and 3.5×10^9/l and platelets above 75×10^9/l, 75% of the initial dose was given.

If WBC remained below 2×10^9/l or platelets below 75×10^9/l for more than 2 weeks the patient was taken off study. If serum creatinine exceeded 180 μmol/l or creatinine clearance fell below 40 ml/min, treatment was also postponed for a maximum of 2 weeks. If renal function recovered within 2 weeks, treatment was resumed with 75% of the initial dose. Otherwise, the patient was taken off study.

Response was assessed according to WHO criteria [13]; a complete response (CR) was defined as the complete disappearance of all known disease, determined by two observations not less than 4 weeks apart; partial response (PR) as at least 50% reduction in the sum of the products of the two largest perpendicular diameters of all measurable lesions, determined by two observations not less than 4 weeks apart; progressive disease (PD) as an increase of at least 25% in any measurable lesion or the appearance of a new lesion; and no change (NC) as less than 50% reduction in total tumour volume or less than 25% increase in any measurable lesion. Response duration was calculated from the start of chemotherapy to the date of first observation of progressive disease.

Patients were evaluable for response if they had completed two cycles of chemotherapy, unless there was rapid early progression. All patients who had received at least one dose of chemotherapy were evaluable for toxicity, which was also graded according to WHO criteria [13].

Statistics

The lowest limit of therapeutic activity considered to be of interest was a response rate of 20%. The patients were entered

Correspondence to R. de Wit.
R. de Wit, M. Tesselaar, C. Seynaeve, C.J. Rodenburg, J. Verweij and G. Stoter are at the Department of Medical Oncology; P.A. Helle is at the Department of Radiotherapy, Rotterdam Cancer Institute/Daniel den Hoed Kliniek, Rotterdam; and T.C. Kok is at the Department of Medical Oncology, University Hospital Rotterdam/Dijkzigt, Rotterdam, The Netherlands.
Revised 6 June 1991; accepted 20 June 1991.

Table 1. Patient and tumour characteristics

	Carboplatin	Iproplatin
Number of patients	15	32
Median age (range)	64 (51–73)	61 (43–74)
Sex		
Male	12	27
Female	3	5
Performance status (WHO)		
0	3	7
1	4	18
2	8	7
Metastatic sites		
Pelvic disease only	–	4
Distant metastases	15	28
Prior surgery	11	26
Prior radiotherapy	8	18

with a maximum number of 30 on each treatment arm in three steps; 14 + 8 + 8. If no responses were obtained in the first 14 patients or less than 2 in the first 22 patients, patient entry was closed for that arm. Thereby it was ensured that if the drug had a response rate of at least 20%, the probability of rejecting the drug erroneously from further study was less than 0.05 [14].

RESULTS

Between December 1986 and November 1989, 48 patients were randomised. 1 patient did not receive chemotherapy because of rapid deterioration of renal function. Patient and tumour characteristics are shown in Table 1.

Of the 47 patients who actually received treatment, 4 patients were not evaluable for response: 2 did not fulfil the criteria for measurable disease, 1 died after one course due to bronchopneumonia and 1 developed an allergic reaction during the first treatment cycle.

14 patients received a median of two (range 2–4) cycles of carboplatin, none of whom achieved a response. 29 patients received a median of two (range 2–6) cycles of iproplatin. 5 patients achieved a PR (17%, 95% confidence interval 4–31%). If all 32 patients who received at least one course of iproplatin were included in this analysis, the response rate would have been 16%. The median duration of response was 27 weeks (range 22–37 weeks). No responses were seen in pelvic masses.

The side-effects were assessed in 47 patients and are summarised in Table 2. The most frequent side-effects encountered were nausea, vomiting and myelosuppression. Vomiting (WHO grade 2–3) was observed in 53% and 84% of the patients treated with carboplatin and iproplatin, respectively, despite prophylactic anti-emetic treatment. Diarrhoea (WHO grade 2) occurred in 1 patient (7%) on carboplatin and in 6 patients (19%) on iproplatin. Thrombocytopenia (WHO grade 3–4) was observed in one third of patients in each arm. 2 patients (13%) treated with carboplatin and 4 (13%) treated with iproplatin required platelet transfusions. 3 patients (20%) on carboplatin developed leukopenic fever requiring antibiotics. This was the case for 1 patient (3%) on the iproplatin arm. Signs or symptoms of nephrotoxicity, ototoxicity and neurotoxicity did not occur. 2 patients developed hypersensitivity reactions to iproplatin [15]. 1 patient exhibited a diffuse skin eruption following the first administration. The hypersensitivity was confirmed by a patch test. Skin biopsy showed an inflammatory reaction with many eosinophils. The other patient had erythema and hypotension after the second administration and had to be treated with plasma infusions and corticosteroids.

Table 2. Side-effects

Side-effects (WHO grade)	Carboplatin (n = 15)	Iproplatin (n = 32)
Vomiting grade 2–3	8 (53)	27 (84)
Diarrhoea grade 2	1 (7)	6 (19)
Thrombocytopenia		
Grade 2	2 (13)	7 (22)
Grade 3–4	5 (33)	11 (34)
Leucocytopenia		
Grade 2	3 (20)	7 (22)
Grade 3–4	3 (20)	1 (3)
Allergic reactions	0	2 (6)

No. (%).

DISCUSSION

This randomised phase II study investigated the clinical usefulness of carboplatin and iproplatin in patients with advanced urothelial cancer. None of 14 evaluable patients treated with carboplatin responded. This finding is in keeping with the 6–21% overall response rate which has been reported in 6 published studies [16–21]. When we add our patients to these series, a total of 20 out of 174 patients have responded (12%). These results demonstrate that carboplatin has only limited activity in urothelial cancer.

Of 29 evaluable patients treated with iproplatin, 5 achieved a PR (17%) for a median duration of 27 weeks. This response rate is in the same range as that reported of single agent cisplatin: of a total of 309 patients who have been treated in phase III studies, 51 have responded, for an overall response rate of 17% (range 9–31%) [1, 3, 22–24].

Although in our study iproplatin did not cause toxicity of the kidney, ear or nervous system, bone marrow toxicity and the chance of hypersensitivity render it unattractive as an alternative to cisplatin.

1. Hillcoat BL, Raghavan D, Matthews J, *et al.* A randomized trial of cisplatin versus cisplatin plus methotrexate in advanced cancer of the urothelial tract. *J Clin Oncol* 1989, 7, 706–709.
2. Yagoda A. The role of cisplatin-based chemotherapy in advanced urothelial tract cancer. *Semin Oncol* 1989, **16** (Suppl. 6), 98–104.
3. Loehrer PJ, Elson P, Kuebler JP *et al.* Advanced bladder cancer: a prospective intergroup trial comparing single agent cisplatin (CDDP) versus M-VAC combination therapy. *Proc Am Soc Clin Oncol* 1990, **9**, 132.
4. Logothetis CJ, Dexeus FH, Finn L, *et al.* A prospective randomized trial comparing M-VAC and CISCA chemotherapy for patients with metastatic urothelial tumors. *J Clin Oncol* 1990, **8**, 1050–1055.
5. Sternberg CN, Yagoda A, Scher HI, *et al.* Methotrexate, vinblastine, doxorubicin and cisplatin for advanced transitional cell carcinoma of the urothelium. Efficacy and patterns of response and relapse. *Cancer* 1989, **64**, 2448–2458.
6. Harker WG, Meyers FJ, Freiha FS, *et al.* Cisplatin, methotrexate and vinblastine (CMV): and effective chemotherapy regimen for metastatic transitional cell carcinoma of the urinary tract. A Northern California Oncology Group study. *J Clin Oncol* 1985, **3**, 1463–1470.
7. Stoter G, Splinter TAW, Child JA, *et al.* Combination chemotherapy with cisplatin and methotrexate in advanced transitional cell cancer of the bladder. *J Urol* 1987, **137**, 663–667.
8. Stark JJ, Howel SB. Nephrotoxicity of cisplatinum (II) dichlorodiammine. *Clin Pharmacol Ther* 1978, **23**, 461–466.

9. Foster BJ, Harding BJ, Wolpert-DeFilippes MK, Rubinstein LY, Clagett-Carr K, Leyland-Jones B. A strategy for the development of two clinically active cisplatin analogs: CBDCA and CHIP. *Cancer Chemother Pharmacol* 1990, **25**, 395–404.
10. Calvert AH, Harland SJ, Newel DR, *et al.* Early clinical studies with cis-diammine-1, 1-cyclobutane dicarboxylate platinum II. *Cancer Chemother Pharmacol* 1982, **9**, 140–147.
11. Creaven PJ, Madajewicz S, Pendyala L, *et al.* Phase I clinical trial of cis-dichloro-trans-dihydroxy-bis-isopropylamine platinum (IV) CHIP. *Cancer Treat Rep* 1983, **67**, 795–800.
12. Van Glabbeke M, Renard J, Pinedo HM, *et al.* Iproplatin and carboplatin induced toxicities: overview of phase II clinical trials conducted by the EORTC early clinical trials cooperative group (ECTG). *Eur J Cancer Clin Oncol* 1988, **24**, 255–262.
13. *WHO Handbook for Reporting Results of Cancer Treatment.* Geneva, World Health Organisation, 1979.
14. Gehan EA. The determination of the number of patients required in a follow-up trial of a new chemotherapeutic agent. *J Chron Dis* 1961, **13**, 346–353.
15. Rodenburg CJ, van Ulsen J, Seynaeve C, Stoter G. Hypersensitivity reactions to CHIP. *J Clin Oncol* 1990, **8**, 1119.
16. Raabe NK, Fosså SD, Parø G. Phase II study of carboplatin in locally advanced and metastatic transitional cell carcinoma of the urinary bladder. *Br J Urol* 1989, **64**, 604–607.
17. Medical Research Council Working Party on Urological Cancer: A phase II study of carboplatin in metastatic transitional cell carcinoma of the bladder. *Eur J Cancer Clin Oncol* 1987, **23**, 375–377.
18. Oliver RTD, Kwok HK, Highman WJ, Waxman J. Methotrexate, cisplatin and carboplatin as single agents and in combination for metastatic bladder cancer. *Br J Urol* 1986, **58**, 31–35.
19. Creekmore SP, Waters WB, Vogelzang NJ, Micetich KC, Fisher RI. Antitumour activity of 24-hour CBDCA infusions in metastatic transitional cell carcinoma. *Proc Am Soc Clin Oncol* 1986, **5**, 101.
20. Marcuello E, Izquierdo MA, Germá JR, *et al.* Carboplatin for advanced bladder cancer. *Eur J Cancer* 1990, **26**, 849–850.
21. Trump DL, Elson P, Madajewicz S and the Eastern Cooperative Oncology Group. A phase II trial of carboplatin in advanced transitional cell carcinoma of the urothelium. In: Bunn PA, Canetta R, Ozols RF, Rozencweig M, eds *Carboplatin.* New York, WB Saunders, 1990, 93–97.
22. Troner M, Birch R, Omura GA, Williams S. Phase III comparison of cisplatin alone versus cisplatin, doxorubicin and cyclophosphamide in the treatment of bladder (urothelial) cancer: a Southeastern Cancer Study Group Trial. *J Urol* 1987, **137**, 660–662.
23. Khandekar JD, Elson PV, DeWys WD, Slayton RE, Harris DT. Comparative activity and toxicity of cis-diamminedichloroplatinum (DDP) and a combination of doxorubicin, cyclophosphamide, and DDP in disseminated transitional cell carcinomas of the urinary tract. *J Clin Oncol* 1985, **3**, 539–545.

Acknowledgements—We thank Mrs Corine Blok for typing the manuscript, and Bristol-Myers Woerden, the Netherlands, for supplying iproplatin.

Eur J Cancer, Vol. 27, No. 11, pp. 1385–1389, 1991.
Printed in Great Britain

0277–5379/91 $3.00 + 0.00

Paternity in Patients with Testicular Germ Cell Cancer: Pretreatment and Post-treatment Findings

Peter Vejby Hansen, Karin Glavind, Jytte Panduro and Mogens Pedersen

Paternity before and after treatment was investigated in 177 patients with unilateral germ cell tumours of the testis. Before the cancer was diagnosed, 51% had fathered at least 1 child, 9% had a history of infertility and 40% had not wanted to have children. It was estimated that 72% of the patients would have fathered at least 1 child at the age of 40 years. After treatment 41 patients had wished to have children. Infertility was still a problem 5 years after the end of treatment in 53% of these men. No significant differences was observed between patients treated with orchiectomy alone and patients treated with cisplatin-based chemotherapy or subdiaphragmatic irradiation. In 8 patients, infertility was present in spite of an evident recovery of spermatogenesis. Congenital malformations were recorded in 3.8% of the live-born children conceived before the orchiectomy. This incidence did not exceed the Danish national rate, the relative risk being 2.5 (95% confidence limits, 0.9–5.5). No malformations were observed in the 22 children conceived after ending treatment.
Eur J Cancer, Vol. 27, No. 11, pp. 1385–1389, 1991.

INTRODUCTION

THE LONG-TERM survival of patients with germ cell tumours of the testis is increasing [1]. Attention has therefore shifted to the physical and psychological consequences of the disease itself and its treatment, and to the question of fertility. The low postorchiectomy sperm counts in testicular cancer patients may in some cases be explained by a history of cryptorchidism or carcinoma *in situ* of the contralateral testis [2, 3]. In most patients, however, the origins of this impairment remains unknown [2]. Gonadal dysfunction should be expected to have impaired fertility before the cancer was actually diagnosed. Treatment with combination chemotherapy and radiotherapy can further impair the spermatogenesis, but sperm production seems to resume in most patients treated for testicular cancer [4, 5]. Prior studies on the paternity before treatment comprise small and selected groups, and little information is available about the actual fertility after treatment [6]. No information is available concerning children fathered prior to the orchiectomy [6], and data on children fathered after treatment are few [7, 8].

Correspondence to P.V. Hansen, Department of Oncology, Aalborg Municipal Hospital, Hobrovej 18–22, DK–9100 Aalborg, Denmark.
P.V. Hansen is at the Danish Cancer Society, Department of Experimental Clinical Oncology, Århus; K. Glavind, J. Panduro and M. Pedersen are at the Departments of Oncology and Clinical Chemistry, Aalborg Municipal Hospital, Aalborg, Denmark.
Revised 13 June 1991; accepted 9 July 1991.