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Acknowledgements—We are grateful to Mrs A.H.W. van den Belt-Dusebout for invaluable help with data retrieval and to Mr A.A.M. Hart for statistical advice.

Eur J Cancer, Vol. 29A, No. 3, pp. 347–350, 1993.
Printed in Great Britain

0964–1947/93 $6.00 + 0.00

A Phase II Study of Cisplatin Plus Methotrexate With Folinic Acid Rescue in Metastatic or Locally Recurrent Transitional Cell Carcinoma of the Urothelium

Poul Flemming Geertsen, Lisa Sengeløv, Susanne Kornum Larsen and Hans von der Maase

34 patients with metastatic or recurrent transitional cell carcinoma (TCC) of the urothelium were treated with cisplatin 100 mg/m² plus methotrexate 250 mg/m² with folinic acid rescue every 3 weeks. A response rate of 55% was achieved with two complete and 15 partial responses in 31 evaluable patients. The overall median survival was 7 months, 9 months for responding and 4 months for non-responding patients. Toxicity was generally moderate. However, 1 patient with previous infectious problems died of neutropenic sepsis. Overall, 83% of the scheduled doses of cisplatin and 96% of the scheduled doses of methotrexate were given. In conclusion, this schedule of the combination of cisplatin and methotrexate did not improve response rate or survival compared with previous studies of this two-drug combination.
Eur J Cancer, Vol. 29A, No. 3, pp. 347–350, 1993.

INTRODUCTION

PATIENTS WITH metastatic transitional cell carcinoma (TCC) of the urothelium have a dismal prognosis with an expected survival of 3–5 months for patients who progress on chemotherapy [1]. Urothelial tract tumours are chemosensitive, but so far long-term benefit is limited to few patients. Cisplatin and methotrexate are considered the most effective single agents with response rates of about 30%, but complete response has been achieved in less than 5% [1, 2]. Combination chemotherapy has been reported to increase the number of patients achieving a complete response, but only the four drug combination M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin) has demonstrated a significant survival benefit over single agent cisplatin in randomised trials [3]. Whether this apparent superiority of the M-VAC

Table 1. Patients' characteristics

No of eligible/evaluable patients	34/31
Age, median (range)	63 (43–74)
Female/male	5/29
Histology	
TCC	30
TCC + squamous cell carcinoma	3
TCC + squamous cell carcinoma + adenocarcinoma	1
Prior therapy	
Cystectomy	11
Nephroureterectomy	5
Radiotherapy—radical	17
Radiotherapy—palliative	2
Instillation (BCG/mitomycin C/doxorubicin)	6
Interleukin-2 + LAK-cells	7
Sites and extent of disease	
Local recurrence only	3
Local recurrence plus metastases	9
Metastases only (the primary removed)	22
Infradiaphragmatic lymph nodes	22
Supradiaphragmatic lymph nodes	9
Lung	11
Liver	4
Bone	8
Skin	2
Brain	2

LAK = Lymphokine activated killer. BCG = Bacillus.

regimen depends upon a higher treatment intensity or the combination of the involved chemotherapeutic drugs is unknown. As neither vinblastine nor doxorubicin possesses major single agent activity in TCC [1] attempts to modify the two drug regimen of cisplatin and methotrexate warranted further investigations. A previous report indicated a high response rate and acceptable toxicity by use of cisplatin 100 mg^2 and methotrexate 200 mg^2 with folinic acid rescue [4].

PATIENTS AND METHODS

Patients

Eligibility criteria were measurable histologically confirmed metastatic or postradiation non-resectable recurrent TCC of the urothelium; performance status 0, 1, 2 (ECOG); no prior chemotherapy; white blood cell (WBC) count above 3×10^9/l and platelet count above 100×10^9/l; [^{51}Cr]EDTA clearance above 50% of the predicted normal value; no other malignancy except basal cell carcinoma; informed consent before initiation of treatment.

Pre-treatment assessments comprised clinical examination, haemoglobin, WBC, platelets, liver function tests, creatinine, glomerular filtration rate (GFR) assessed by use of [^{51}Cr]EDTA clearance, X-ray of the chest, computed tomography scan of the abdomen, and biopsy verification of metastatic disease.

34 patients entered the protocol. 30 patients had metastatic disease, 1 patient with a previously removed renal pelvic tumour had regional lymph node metastasis and 3 patients had a non-resectable local recurrence after radiotherapy. Table 1 gives the patients' characteristics. 7 patients entered the protocol following failure of immunotherapy with recombinant interleukin-2 plus LAK-cells [5]. 17 had received prior radical radiotherapy and 11 have had a cystectomy.

Treatment

Cisplatin 100 mg/m^2 followed by methotrexate 250 mg/m^2 at the same day were given every 3 weeks. The treatment was stopped in case of unacceptable toxicity or progressive disease (PD), after six courses in case of no change (NC) and after nine courses in case of partial (PR) or complete response (CR).

Administration of cisplatin was preceded by infusion of 1 l of dextrose/saline and 0.5 l mannitol 20% within 1.5 h. Cisplatin was reconstituted in 0.5 l isotonic saline and given in 0.5 h followed by 1 l of dextrose/saline within 1.5 h. Methotrexate reconstituted in 0.5 l dextrose was given in 0.5 h followed by 1 l of dextrose/saline within 1.5 h. Folinic acid (Leucovorin) rescue treatment started after 24 h. The dose was 15 mg given orally every 6 h for a total of eight times. Sodium citrate was given from day 1 to 4 to keep the urine alkaline. Antiemetic treatment was given prophylactically. The treatment consisted in most cases of metoclopramide 2 mg/kg given as a bolus injection and lorazepam 1–2 mg given orally 0.5 h before cisplatin, followed by continuous infusion of metoclopramide 5 mg/kg within 8 h.

Dose modifications

The initial cisplatin dose was reduced to 75% of the scheduled dose in patients with a [^{51}Cr]EDTA clearance within 50–75% of the predictive normal value. During treatment, the cisplatin dose was reduced by 50% of the initial dose in case of a more than 33% reduction of the [^{51}Cr]EDTA clearance. No further cisplatin was given in case of a more than 50% reduction of the [^{51}Cr]EDTA clearance. Methotrexate was reduced according to WBC and platelet counts and cisplatin according to platelet counts. Nadir WBC count $< 1 \times 10^9$/l and/or platelet count $< 50 \times 10^9$/l resulted in a dose reduction of 33% in the subsequent course. Treatment was delayed for 1 week in case of WBC count $< 2 \times 10^9$/l and/or platelet count $< 50 \times 10^9$/l at the treatment day. The doses were reduced to 67% in case of treatment day values of WBC of $2–3 \times 10^9$/l and/or platelets of $50–100 \times 10^9$/l.

Evaluation of toxicity

The haematological hepatic and renal toxicities were recorded according to WHO criteria [6]. Clinical and biochemical assessments were repeated before each course of chemotherapy. [^{51}Cr]EDTA clearance was routinely repeated after every third course, and before each course in patients with serum creatinine above 130 μmol/l or reduced [^{51}Cr]EDTA clearance.

Evaluation of response to treatment

Full reassessment of evaluable disease was performed after every third cycle. The response categories were defined according to WHO criteria [6]. Patients dying early, i.e. before the first planned evaluation of response were included as having PD.

RESULTS

34 patients entered the study. All patients were eligible and evaluated for toxicity. 1 patient died as a result of neutropenic sepsis after the first course and 2 patients refused evaluation of response after three courses of chemotherapy. Accordingly, 31 patients were evaluable for response. 17 of 31 evaluable patients

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Revised 9 June 1992; accepted 22 June 1992.

responded to treatment, the overall response rate being 55% (95% confidence limits 36–73%). 2 patients had a CR and 15 patients a PR. 6 patients had NC and the remaining 8 patients progressed within the first three courses of chemotherapy.

Response duration for the 2 patients achieving CR was 4 months and 13 months, respectively. The median response duration for patients with PR was 6 months (range 119–422 days). Table 2 shows the response by site of disease. No response was seen in bone metastases and only 2 out of 12 patients with local recurrences responded. 1 of 3 evaluable patients with a mixed tumour histology obtained a PR. 1 patient with brain and lung metastases obtained CR following chemotherapy alone. Relapse occurred in the brain after 13 months. The patient survived for 17 months without evidence of systemic relapse. The second patient with brain metastases died early before response evaluation. All patients but 1 have died. The overall median survival was 7 months (range 7–532 days), 9 months for responding and 4 months for non-responding patients. 5 patients died early and treatment was stopped in additional 3 patients because of PD before the first planned evaluation after three courses. Prior treatment with interleukin-2 and LAK-cells was not correlated to survival or response to chemotherapy.

A total of 182 courses were given. Overall, 83% of the scheduled dose of cisplatin and 96% of the scheduled doses of methotrexate were given. The main causes for dose reductions were haematological toxicity and nephrotoxicity. The haematological toxicity was moderate, demanding dose reduction in 4 patients. 9 patients had grade 3 and 2 patients grade 4 leukopenia. Only 1 of these cases was associated with fever. This patient died of bacterial sepsis. The patient had a long febrile period prior to therapy and treatment with antibiotics was initiated 2 days after chemotherapy due to bacteraemia.

Nausea and vomiting were common but in general limited to grade 1 and 2. Stomatitis (grade 1–3) occurred in 9 patients. 6 patients complained of mild peripheral sensory neuropathy. Reversible tinnitus was experienced by 13 patients but none had symptomatic hearing loss. Audiometric assessment was not performed routinely. Alopecia was limited to grade 0 or 1 in all patients. 6 patients entered the protocol with a more than 25% reduction of the GFR and were given 75% of the scheduled cisplatin dose in the first cycle. A further dose reduction due to nephrotoxicity was only necessary in one of these patients. An additional 7 patients had their cisplatin doses reduced during treatment because of a more than 33% reduction of the [^{51}Cr]EDTA clearance. Following dose reduction of cisplatin only 2 of these 13 patients had a further decline in the GFR. 1 patient had a more than 50% reduction of the GFR and was given carboplatin instead of cisplatin in the last course. None of these 13 patients had serum creatinine levels above 200 μmol/l (WHO grade 1).

Table 2. Response by site of metastatic disease

Site	No.	CR	PR	Response (%)
Local recurrences	12	0	2	17
Infradiaphragmatic lymph nodes	22	4	9	59
Supradiaphragmatic lymph nodes	9	2	6	89
Lung	11	2	4	55
Liver	4	1	2	75
Bone	8	0	0	0
Skin	2	1	1	100
Brain	2	1	0	50

DISCUSSION

The response rate was 55% (95% confidence limits 36–73%) with a CR rate of 6%. The overall response rate was higher than previous single agent studies of cisplatin and methotrexate, but the CR rate (6%) and median overall survival (7 months) was not improved [1]. These findings were corroborated by a randomised study of cisplatin 80 mg/m^2 every 4 weeks versus cisplatin 80 mg/m^2 day 2 plus methotrexate 50 mg/m^2 day 1 and 15 every 4 weeks in which no difference in either CR rate or overall survival were observed [7]. In other studies of cisplatin and methotrexate, CR rates of 15% to 23% have been reported [4, 8, 9], but the overall survival figures were similar to our results. Carmichael *et al.* treated 19 patients with a 3-weekly combination of cisplatin 100 mg/m^2 and methotrexate 200 mg/m^2 with folinic acid rescue and reported an overall response rate of 68% with a CR rate of 21% [4]. The 95% confidence limits are, however, broad in these small studies. Compared with the three-drug combinations of cisplatin, doxorubicin and cyclophosphamide (PAC/CISCA) and cisplatin, methotrexate and vinblastine (CMV) the CR rate in the present study was inferior but the overall survival was similar [10, 11].

The M-VAC regimen has produced CR rates of 13% to 35% and overall median survival figures of 12 to 15 months [3, 11, 12]. Others have attempted to reduce the toxicity of the M-VAC regimen by replacing cisplatin and doxorubicin with carboplatin and mitoxantrone [13]. A CR rate of 27% was achieved and although the reported follow-up period was short, these and the M-VAC results are important because they indicate that drugs with only moderate single agent activity, i.e. carboplatin, doxorubicin and vinblastine [1, 8], may play an important role in the combined regimens.

Our approach of increasing the dose-intensity of the combined cisplatin/methotrexate regimen did not improve the response rate. As the administered dose of cisplatin was either comparable with or higher than the scheduled dose in several of the cited studies the benefit of the present schedule of methotrexate demanding folinic acid rescue has to be questioned. On the other hand, this methotrexate schedule with folinic acid rescue was probably responsible for the relatively mild toxicity, which makes it possible to include additional drugs without reducing the doses of the present ones. Thus, the treatment was well tolerated. The haematological toxicity was generally moderate. 1 patient died of neutropenic sepsis but this patient had pre-existing infectious problems. 9 patients experienced grade 3 and 2 patients grade 4 leukopenia. Renal toxicity was well handled by use of GFR measurements after every third cycle and no WHO grade 2–4 toxicity was observed.

In conclusion, the present schedule of cisplatin 100 mg/m^2 plus methotrexate 250 mg/m^2 every third week is effective in metastatic TCC, but not better than other cisplatin and methotrexate combination schedules.

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Eur J Cancer, Vol. 29A, No. 3, pp. 350–354, 1993.
Printed in Great Britain

0964–1947/93 $6.00 + 0.00

Phase II Study of Pirarubicin (THP) in Patients with Cervical, Endometrial and Ovarian Cancer: Study of the Clinical Screening Group of the European Organization for Research and Treatment of Cancer (EORTC)

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From 1986 to 1990, a multicentric phase II study was conducted with pirarubicin, a new semi-synthetic anthracyclin [4′-*O*-tetrahydropyranyl-adriamycin (THP)]. 87 patients with advanced gynaecological cancers were treated: epidermoid cervical carcinoma (n = 31), adenocarcinoma of the endometrium (n = 28) and ovarian adenocarcinoma (n = 28). THP was administered by short intravenous infusion, for 3 consecutive days, every 3 weeks. The initial dose of THP was 25 mg/m² day (25% of patients) which was then reduced to 20 mg/m² day. The average number of courses was 3.7 (range 1–10). The cumulative THP dose was 180 mg/m² (range 56–594) in cervix and endometrial tumours and 121 mg/m² (range 58–425) in ovarian tumours. Myelosuppression was the major observed toxicity with grade 3–4 leukopenia and thrombocytopenia in 62 and 19% of the patients, respectively. Severe general complications occurred in 6% of the patients with three fatalities due to infections. Gastro-intestinal side-effects were frequent and usually mild (7% of grade 3 vomiting). 48% of the patients showed alopecia, which was complete in 9 cases (10%). 3 patients experienced cardiac events. No significant antitumoral activity was observed in patients who had failed to respond to previous chemotherapy. Promising antitumoral activity was noticed in untreated cervico–uterine carcinomas with 19% partial responses and 12% complete responses (CR). THP activity was lower in endometrial carcinomas (9.5% CR). Results were found to be negligible in ovarian cancer patients, most of them being refractory to previous chemotherapy containing an anthracyclin compound. On the basis of these results, the definite role of THP in gynaecological cancers deserves to be studied in more favourable programmes (e.g. in combined protocols as first-line chemotherapy).
Eur J Cancer, Vol. 29A, No. 3, pp. 350–354, 1993.

INTRODUCTION

PIRARUBICIN [4′-*O*-tetrahydropyranyl-adriamycin (THP)] is a semi-synthetic analogue of doxorubicin and chemically resembles other anthracyclins [1, 2]. It acts by inhibiting DNA synthesis via intercalation or direct interaction with DNA polymerase and topoisomerase II. It also acts by generating free radicals and modifying membraneous phospholipids [3]. THP blocks the cell cycle in phase G2. In experimental models, THP antitumoral activity was found to be at least equivalent to that of doxorubicin [4] and showed a higher and faster intracellular uptake [5, 6] and less pronounced myocardial, capillary [7] and biological [8] toxicities.