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CLINICAL TRIAL REPORT

Ian N. Olver · Jennifer Stephenson · Doreen Schulze

A phase I study of prolonged ambulatory infusion carboplatin with oral etoposide showing activity in prostate cancer

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Abstract *Purpose*: This phase I study aimed to establish the dose for phase II trials of a dose-intense outpatient regimen of ambulatory carboplatin and oral etoposide. *Patients and Methods*: Cohorts of three patients received escalating doses of carboplatin 15, 20, and 23 mg/m^2/day as a 3-week continuous ambulatory infusion with oral etoposide initially at 50 mg/day. Patients entered had prostate, colon, head and neck, breast, unknown primary cancers and mesothelioma. *Results*: At 23 mg/m^2 of carboplatin, two patients had WHO grade 3 lethargy and myelosuppression, which were the dose-limiting toxicities. Six patients were entered at the dose recommended for phase II studies, carboplatin 20 mg/m^2/day and etoposide 50 mg/day for 21 days repeated every 6 weeks. This was well tolerated except for one patient with multiple bone metastases from prostate cancer experiencing grade 4 myelosuppression and a single patient with grade 3 constipation. Seven patients with hormone-resistant prostate cancer were entered into the study, one at 15 mg/m^2, four at 20 mg/m^2 and two at 23 mg/m^2 of carboplatin, and received a median of four cycles of treatment. The only responses were seen in prostate cancer where there were two partial responses in patients with soft tissue predominant disease. Five patients who could be evaluated with initially elevated PSA exhibited falls of ≥50% after receiving the chemotherapy. All but one patient with prostate cancer experienced significant reduction in pain levels. The median time to progression of the patients with prostate cancer was 4 months. *Conclusions*: Ambulatory infusion carboplatin and oral etoposide is a tolerable dose-intense outpatient regimen which warrants further testing in phase II trials including hormone-resistant prostate cancer.

Key words Phase I · Infusion · Carboplatin · Etoposide · Prostate

Introduction

Carboplatin is an analogue of cisplatin with a broad spectrum of activity which includes ovarian, germ cell, head and neck and lung cancers but exhibiting less nephrotoxicity, ototoxicity, peripheral neuropathy and gastrointestinal toxicity [3]. The original phase I studies established a dose for phase II trials as 400 mg/m^2 but the area under the concentration time curve (AUC) for carboplatin was found to be dictated primarily by the glomerular filtration rate and dose, and this relationship is now used to guide dosing [2]. The maximum tolerated dose of carboplatin has little schedule dependency, but preclinical data suggested that prolonged exposure enhanced cytotoxicity [7].

When carboplatin was infused continuously for up to 5 days, a final dose of 2100 mg/m^2/5 days was reached in a phase I study, with significant myelosuppression but little extramedullary toxicity [15]. A phase I study of a 21-day continuous ambulatory infusion of carboplatin identified a maximum tolerated dose of 30 mg/m^2/day, which could be repeated every 6 weeks. Myelosuppression was the dose-limiting toxicity [22]. We previously performed a phase I and pharmacokinetic study of prolonged ambulatory infusion carboplatin over 6 weeks which identified a dose-intense outpatient regimen suitable for concomitant use with radiotherapy [18].

Etoposide is another agent with a broad spectrum of activity including lung cancer, acute non-lymphocytic leukaemia and germ cell tumours. Giving high bolus doses or low doses continuously has intensified the dose, and schedule dependency has been shown [8]. Etoposide can be administered by the intravenous or oral route. The maximum tolerated dose of oral etoposide over

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I. N. Olver (✉) · J. Stephenson · D. Schulze
Royal Adelaide Hospital Cancer Centre,
North Terrace, Adelaide South Australia, Australia 5000
e-mail: iolver@medicine.adelaide.edu.au
Tel.: +61-8-82225577; Fax: +61-8-82322148

21 days was 50 mg/m^2/day, and twice daily dosing may be more effective [8,10]. Myelosuppression was the dose-limiting toxicity.

The combination of carboplatin and etoposide has been found to be efficacious in lung cancer, germ cell tumours, gynaecological malignancies, breast cancer, childhood solid tumours and cancers of unknown primary origin [16, 1, 14, 9, 20, 24]. Our trial aimed to establish an intensive outpatient combination of these drugs. The maximum tolerated dose and dose-limiting toxicities of carboplatin as a prolonged ambulatory infusion with etoposide in continuous oral dosing were the primary end points of the trial.

Patients and methods

Eligibility

Patients with histologically confirmed malignancy and measurable or evaluable disease who had an ECOG performance status of 0–2 were eligible for entry into the study. Prior chemotherapy and radiotherapy must have been completed 4 weeks before study entry (or 6 weeks following nitrosoureas) and the patient must have recovered from all previous toxicities. Previous radiotherapy must have been limited to less that 50% of bone marrow-producing areas. Serious concomitant medical or surgical illnesses or malignancies other than surgically treated basal cell carcinoma of the skin or carcinoma in situ of the cervix excluded patients from study entry. Patients required adequate bone marrow function, defined as hemoglobin >11 g/dl, absolute neutrophil count $>2000/\mu$L and platelet count $>100{,}000/\mu$L. Patients were required to have levels of liver transaminases within twice the upper limit for normal and creatinine at <0.13 mmol/L. Due to the requirement for an ambulatory infusion pump, patients had to be judged able to care for the pump and be geographically accessible for follow-up. The protocol was approved by the Royal Adelaide Hospital ethics committee to be conducted according to good research practice guidelines, and all patients were required to give written informed consent prior to study entry.

Treatment

Cohorts of three patients received escalating doses of carboplatin given as a continuous ambulatory infusion, by a pump connected to a venous access device, over 3 weeks with etoposide given by mouth either in single or twice daily doses depending on the total daily dose. Dose escalation was not planned in individual patients. Carboplatin dose levels commenced at 15 mg/m^2/day and were to be escalated to 20 mg/m^2/day, then 23 mg/m^2/day. Etoposide was commenced at 50 mg/day with the initial three dose levels of carboplatin, with a plan to escalate to 100 mg/day at the 23 mg/m^2 carboplatin and beyond. Further escalation of the carboplatin was planned to 27 mg/m^2/day, then in increments of 25% until a dose-limiting toxicity defined the maximum tolerated dose (MTD).

The MTD was defined as a dose level at which two patients experienced grade 3 or 4 toxicities (with the exception of alopecia). A further three patients were to be entered at the dose level below the MTD, to further define the toxicities at the dose to be recommended for phase II studies. Courses were repeated in 21 days if patients had recovered from the toxicity of the previous course. If not, the treatment was delayed and the dose could be reduced by 25%. Treatment was planned to continue until maximum response. Two further cycles were allowed after achieving a complete response. Patients discontinued the chemotherapy if their disease progressed, they had unacceptable toxicity, developed a serious concomitant illness or requested withdrawal.

Pretreatment evaluation included a history and physical examination, electrocardiograph, complete blood examination, electrolytes, renal and liver function tests. X-rays, nuclear medicine scans and CT scans documented the extent of disease. The blood tests, physical examination and toxicity evaluations were performed weekly throughout the study. The appropriate scans to evaluate the disease were repeated every three courses or earlier if clinically indicated.

Results

Thirteen patients received a median of three cycles of chemotherapy at three dose levels of carboplatin, 15, 20, and 23 mg/m^2/day (Table 1). The dose-limiting toxicities on cycle one at the maximum tolerated dose of carboplatin 23 mg/m^2/day and etoposide 50 mg daily were WHO grade 3 neutropenia in two patients and grade 3 lethargy in three patients (Table 2). Six patients were entered at the 20 mg/m^2/day carboplatin with 50 mg/day etoposide, which is the recommended dose for phase II. The only severe toxicities recorded at 20 mg/m^2/day were one of six patients with grade 4 neutropenia, grade 4 thrombocytopenia and one other patient with grade 3 constipation.

Seven of the patients entered into the trial had hormone-resistant prostate cancer. In all patients the insensitivity to hormones was manifested by new metastases with six of the seven also having a rise in PSA (prostate-specific antigen). At study entry, two patients had bone only disease, three bone and liver metastases, one bone and lymph node metastases, and there was one patient with only nodal metastases. All patients had had bilateral orchidectomy as a prior treatment, six had also received an antiandrogen, and four patients had received previous radiotherapy. Two continued on hormone treatment and the chemotherapy was added.

The only objective responses were two partial responses seen in patients with prostate cancer treated at carboplatin doses of 20 mg/m^2/day and 23 mg/m^2/day. One had disease in the liver and the other in the liver and subcutaneous tissues. The relapse-free survivals of the

Table 1 Patient Characteristics

Characteristics	Number
Patients entered	13
Sex	
Males	10
Females	3
Median Age (range) yrs	64 (41–71)
ECOG PS	
0	3
1	7
2	3
Number of cycles	
1	5
2	1
3	3
4	2
5	2

Table 2 Toxicities

Patient number	Dose level carboplatin (mg/m^2/day)	Disease	Drug related toxicity in cycle 1 WHO grade		
			2	3	4
1	15	Prostate	Nausea Anaemia Leucopenia	–	–
2	15	Head + neck	Leucopenia	Alopecia	–
3	15	Colon	Nausea	–	–
4	20	Colon	Alopecia Lethargy	Constipation	–
5	20	Prostate	Bladder	–	–
6	20	Unknown Primary	Leucopenia	–	–
7	23	Prostate	Anaemia	Leucopenia Lethargy	Thrombocytopenia
8	23	Prostate	Lethargy	–	–
9	23	Breast	Diarrhoea	–	–
10	23	Mesothelioma	Nausea	Lethargy Leuocopenia	–
11	20	Prostate	Peripheral Neuropathy Leucopenia Rash Bladder	–	–
12	20	Prostate	–	–	–
13	20	Prostate	Nausea	–	Neutropenia Thrombocytopenia

two were 1 and 7 months, respectively, while the median time to progression of the seven patients with prostate cancer was 4 months (range 1–7 months).

The first of the patients with prostate cancer treated at the 15 mg/m^2/day level of carboplatin was withdrawn before reassessment of PSA when he developed a spinal cord compression at 4 weeks. Of the others, one of the partial responders had a normal PSA pretreatment, but the other five patients with initially raised PSA concentrations exhibited falls of ≥50% on the chemotherapy (Table 3).

All but the initial patient with prostate cancer experienced significant reductions in pain levels. One patient with liver pain reported reduction in the pain from grade 2 to grade 1 by the completion of the first cycle of treatment. The other five patients had complete resolution of pain and required no analgesia by the end of the first cycle at 6 weeks.

Table 3 Prostate-Specific Antigen (PSA)

Patient Number	Pretreatment PSA (ng/ml)	Lowest PSA (ng/ml)
1	>1000	–
5	35.6	2.8
7	2.5	2.4
8	64.0	32.1
11	356.0	48.9
12	254.8	99.1
13	527.3	60.5

Discussion

This study establishes a well-tolerated, dose-intense regimen of prolonged infusion carboplatin with oral etoposide, which is designed for outpatient use. Prolonged infusions have the advantage that toxicity can be more easily remedied by stopping the infusion. However, no dose-limiting nonhaematological toxicity was apparent.

There are many tumour types for which the efficacy of the two drugs in combination has been established, and phase II studies of the prolonged infusion schedule could be justified. In a randomised trial in non-small cell lung cancer, efficacy and survival were improved when intravenous bolus carboplatin was added to continuous oral etoposide as compared to the oral etoposide alone [12].

The unexpected finding of efficacy in prostate cancer in this study warrants further phase II testing. Single agent etoposide has a modest record in prostate cancer. Crawford et al. gave 50 mg/day of oral etoposide for 20 days to 18 patients with prostate cancer and recorded falls in prostate-specific antigen (PSA) in three patients and improvements in bone pain in three others [6]. Hussain et al. gave 50 mg/m^2/day for 21 days to 190 patients with prostate cancer and 1 of 2 with measurable disease had an objective response while 5 others had lowering of PSA concentrations [11]. A 53% objective response rate has been reported for oral etoposide in combination with estramustine [19].

There is only limited efficacy reported for carboplatin in hormone-resistant prostate cancer. Canobbio et al.

reported a 9% objective response rate with 32% stable disease [4]. A response in prostate cancer has been reported for carboplatin in combination chemotherapy in a phase I study [17].

The evaluation of the response of prostate cancer to chemotherapy will be influenced by the prior hormone therapy. Continuing androgen deprivation may be essential in maintaining the response to chemotherapy [5]. In our study the two patients with objective responses had discontinued hormone treatment prior to starting chemotherapy, which raises the possibility of an endocrine withdrawal response. However, two of the patients (8 and 11) who exhibited large falls in PSA concentrations (Table 3) had the chemotherapy added to their endocrine treatment. This factor should be monitored in a phase II trial to further evaluate the efficacy of ambulatory carboplatin and oral etoposide in hormone-resistant prostate cancer.

Objective responses measured in extraosseous disease may not reflect the impact on the more common bone metastases or upon the quality of a patient's life. The use of PSA as a surrogate endpoint in predicting a survival advantage has been questioned in preclinical studies but reported as useful in hormone-refractory prostate cancer treated with chemotherapy [21, 13, 23]. In the current trial there were decreases in PSA concentration of 50% or greater in five of seven patients with prostate cancer. Objective assessment of improved symptom control indicated that responding patients' pain reduced markedly within the first cycle of treatment.

Ambulatory carboplatin and oral etoposide is a dose-intense regimen that was well tolerated on an outpatient basis. A dose has been identified for phase II trials of this regimen. Our preliminary data suggest that these studies should include hormone-resistant prostate cancer.

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