

## Topotecan in combination with carboplatin: phase I trial evaluation of two treatment schedules

A. B. Simpson<sup>1\*</sup>, P. M. Calvert<sup>2</sup>, J. A. Sludden<sup>1</sup>, A. V. Boddy<sup>2</sup>, M. J. Griffin<sup>2</sup>, A. Schätzlein<sup>1</sup>, P. Wilson<sup>1</sup>, K. Fishwick<sup>2</sup>, A. Wheatley<sup>3</sup>, G. A. Ross<sup>3</sup>, A. H. Calvert<sup>2</sup> & C. J. Twelves<sup>1†</sup>

Cancer Research Campaign Departments of Medical Oncology, <sup>1</sup>Glasgow and <sup>2</sup>Newcastle-upon-Tyne; <sup>3</sup>SmithKline Beecham, Harlow, Essex, UK

Received 21 March 2001; revised 23 August 2001; accepted 10 September 2001

### Background

Topotecan and cisplatin combinations have shown schedule-dependent toxicity, which may in part be due to cisplatin nephrotoxicity. As carboplatin is less nephrotoxic and increasingly replacing cisplatin in clinical practice, the aim of this study was to define the optimal sequence and dose for topotecan in combination with carboplatin.

**Patients and methods:** Two parallel phase I trials, with pharmacokinetic studies, were conducted administering carboplatin on day 1 with topotecan on days 1–5 (schedule A) or days 8–12 (schedule B), repeated every 3 weeks.

**Results:** Twenty-one patients were treated over two dose levels, carboplatin AUC 4 [glomerular filtration rate (GFR) calculated from <sup>51</sup>Cr-EDTA clearance] with topotecan 0.5 or 0.75 mg/m<sup>2</sup>. At the first dose level, six patients were evaluable for each schedule. With schedule A, from 34 cycles, there were two dose reductions and 10 treatment delays due to myelosuppression. With schedule B from 25 cycles, there was one reduction and 10 delays. At dose level 2, both patients in schedule A had dose-limiting neutropenia. In contrast, there was no dose-limiting toxicity with schedule B in six patients, although the majority of cycles were delayed.

**Conclusion:** The combination of topotecan and carboplatin using these 3-weekly schedules lead to significant myelotoxicity with attendant dose reductions and delays; the optimal scheduling of these agents remains to be defined.

**Key words:** carboplatin, chemotherapy, topotecan

### Introduction

Topotecan and cisplatin are synergistic in preclinical models [1] and active in similar tumour types. Moreover, their toxicity profiles are complementary, leading to speculation that this may be a potent combination. However, in phase I studies, dose-limiting myelosuppression occurred at relatively low doses [2–4]. One study addressed the impact of cisplatin scheduling [3]. Cisplatin given on the first day of 5 days of topotecan treatment induced more severe myelosuppression than when given on day 5. Pharmacokinetic studies suggested this could be due to reduced clearance of topotecan when given after cisplatin, possibly secondary to subclinical cisplatin nephrotoxicity.

Carboplatin is more myelotoxic than cisplatin, but its lesser nephrotoxicity might permit administration of higher doses. The aim of these two phase I studies was to define a dose and schedule of carboplatin with topotecan for phase II trials. The two studies addressed the impact of administering carboplatin and topotecan on the same or separate days.

### Patients and methods

Parallel studies opened in January 1997. Schedule A: carboplatin on day 1 with topotecan on days 1–5 (Newcastle-upon-Tyne, UK). Schedule B: carboplatin on day 1 with topotecan on days 8–12 (Glasgow, UK).

Toxicity was assessed according to NCI CTC criteria (v. 1.0). Although not primary endpoints, response according to World Health Organization (WHO) criteria and survival were also recorded.

### Patient eligibility

Patients were 18 years or older, with histologically confirmed tumours. Entry required Eastern Cooperative Cancer Group (ECOG) performance status <2, adequate bone marrow reserve [haemoglobin  $\geq$ 9 g/dl, white blood cell (WBC) count  $\geq$ 4000 cells/ $\mu$ l, neutrophils  $\geq$ 1500 cells/ $\mu$ l and

\*Present address: Wellington Cancer Centre, Wellington, New Zealand.

†Correspondence to: Dr C. J. Twelves, CRC Department of Medical Oncology, Alexander Stone Building, Garscube Estate, Switchback Road, Bearsden, Glasgow G61 1BD, UK. Tel: +44-141-211-1712; Fax: +44-141-211-1869; E-mail: c.twelves@beatson.gla.ac.uk

platelets  $\geq 100\,000/\mu\text{l}$ ], renal function (serum creatinine  $< 150\ \mu\text{M/l}$  and  $^{51}\text{Cr-EDTA}$  clearance  $\geq 60\ \text{ml/min}$ ) and bilirubin  $< 2\ \text{mg/dl}$ . Serum transaminases were to be  $< 2.5 \times$  the upper limit of normal (ULN) in the absence of liver metastases, or  $< 5 \times$  the ULN if liver metastases were present. Alkaline phosphatase was to be  $< 2.5 \times$  the ULN in the absence, or  $< 5 \times$  the ULN in the presence, of liver or bone metastases.

Those patients who had received chemotherapy (except adjuvant treatment completed at least 6 months earlier) were excluded, as were those who had undergone extensive radiotherapy that could seriously compromise bone marrow function. Patients receiving concurrent chemotherapy, immunotherapy, radiotherapy or other investigational therapy were ineligible. Those with severe medical problems, or other contraindications to platinum or camptothecins, were also excluded.

Both studies were conducted according to the Declaration of Helsinki and approved by the hospital ethics committees. Written informed consent was obtained before study entry.

### Drugs and administration

Carboplatin doses were individualised according to  $^{51}\text{Cr-EDTA}$  clearance [5], and administered on day 1 of each cycle. Topotecan was given for five successive days, either on days 1–5 or days 8–12. Both cytotoxics were given as 30 min infusions. A 21 day treatment cycle was planned, with delays of up to 2 weeks possible. Owing to treatment delays in the first cohort, the protocol was amended to permit re-treatment when the neutrophil count was  $\geq 1000\ \text{cells}/\mu\text{l}$  and platelet count was  $\geq 75\,000\ \text{cells}/\mu\text{l}$ .

### Dose-limiting toxicity and maximum tolerated dose

Haematological dose-limiting toxicity (DLT) was defined as grade IV neutropenia or thrombocytopenia, lasting  $> 5$  days or complicated by infection or bleeding. Granulocyte colony-stimulating factor (G-CSF) was not given prophylactically. Anti-emetics were given according to local practice. Non-haematological DLT was defined as at least grade III toxicity, excepting nausea, vomiting and alopecia.

### Dose escalation

Carboplatin AUC  $4\ \text{mg/ml-min}$  was given 3-weekly, as this was considered the minimal dose intensity desirable in a combination regimen. Topotecan was given at  $0.5\ \text{mg}/\text{m}^2$  in the first dose level, and escalated to  $0.75\ \text{mg}/\text{m}^2$  for the second level.

### Pharmacokinetics

Samples were collected during the first cycle.

*Carboplatin.* Samples were taken 5 min pre-infusion, mid-infusion and end-infusion, then at 30, 90, 120 min, 4, 6, 8 and 24 h post-infusion. Carboplatin was assayed by atomic absorption spectrophotometry [6].

*Topotecan.* Samples were taken during the first day of topotecan administration pre-infusion, 25, 20 and 15 min before the end of the infusion, end-infusion, then at 15, 30, 60 min, 2, 3, 4 and 6 h post-infusion. Further samples were taken 2 h post-infusion on remaining days according to a limited sampling model [7]. Open and closed lactone ring forms of topotecan were assayed by high performance liquid chromatography (HPLC) [8].

### Data analysis

Analysis with WinNonlin™ (Pharsight Corp., Mountain View, CA, USA) was non-compartmental, using the log-linear trapezoid method with extrapolation.

**Table 1.** Patient demographics

	Schedule A	Schedule B
Evaluable patients	7	12
Median age, years (range)	53 (26–58)	64 (51–75)
Male	2	8
Female	5	4
Performance status		
0	5	3
1	2	9
Prior chemotherapy	3	0
Prior radiotherapy	2	1
Pathology		
ACUP		3
SCLC		3
NSCLC		4
Colorectal	3	1
Squamous		1
Mesothelioma	2	
Melanoma	1	
Endometrial	1	

ACUP, adenocarcinoma of unknown primary; SCLC, small-cell lung cancer; NSCLC, non-small-cell lung cancer.

## Results

### Patients and treatment

Twenty-one patients were entered between January 1997 and January 1998 (Table 1). Three had received prior adjuvant 5-fluorouracil chemotherapy, two prior chest wall radiotherapy, and one limited field palliative radiotherapy.

*Schedule A.* Dose level 1: One patient died from disease progression within 2 weeks of study entry and was replaced. The remaining six received 34 cycles of chemotherapy (median six, range four to six). Dose level 2: Two patients were treated, although one progressed during cycle one and stopped treatment; the other completed six cycles.

*Schedule B.* Dose level 1: six patients received 25 cycles (median 4.5, range two to six). One was withdrawn due to deteriorating renal function (EDTA clearance decreased from 68 to 40 ml/min after completion of two cycles); urinalysis and renal tract ultrasound were normal. Dose level 2: six patients received 20 cycles (median 3.5, range one to six).

### Haematological toxicity

The median platelet nadir occurred later with schedule B than with schedule A (day 21 and 15, respectively;  $P < 0.01$ ). There was a similar trend for neutrophils (median nadir day 19.5 and 18, respectively;  $P = 0.07$ ). No patient received G-CSF.

**Table 2.** Pharmacokinetics of carboplatin (AUC 4) and topotecan (0.5 mg/m<sup>2</sup>) (mean ± standard deviation)

Pharmacokinetic parameter	Schedule		P value
	A	B	
Topotecan closed lactone ring			
AUC (nmol/l-h)	17.36 ± 5.77	23.45 ± 3.49	0.05
Cl (l/h)	123.7 ± 38.5	84.65 ± 11.03	0.04
MRT	1.63 ± 0.75	1.74 ± 0.45	0.76
C <sub>max</sub> (nmol/l)	13.45 ± 5.48	18.63 ± 3.97	0.09
T <sub>max</sub> (h)	0.53 ± 0.04	0.46 ± 0.16	0.33
V <sub>ss</sub> (l)	196.9 ± 91.8	120 ± 55.9	0.11
T <sub>1/2</sub> <sup>β</sup>	1.55 ± 0.61	1.75 ± 0.69	0.60
Topotecan open lactone ring			
AUC (nmol/l-h)	42.82 ± 10.66	70.10 ± 18.76	0.01
Cl (l/h)	43.8 ± 6.98	29.88 ± 9.24	0.02
MRT	3.26 ± 0.53	3.15 ± 0.72	0.78
C <sub>max</sub> (nmol/l)	14.57 ± 1.92	22.01 ± 5.98	0.02
T <sub>max</sub> (h)	0.53 ± 0.04	0.62 ± 0.22	0.33
V <sub>ss</sub> (l)	144.2 ± 42.3	90.5 ± 22.3	0.02
T <sub>1/2</sub> <sup>β</sup>	2.34 ± 0.58	2.41 ± 0.38	0.82
Total topotecan			
AUC (nmol/l-h)	60.18	93.55	0.01
Carboplatin			
GFR ml/min	135 ± 36	98 ± 24	0.04
AUC mg/ml-min	4.6 ± 1	4.1 ± 0.4	0.20
Target AUC	115 ± 24	102 ± 10	0.17
Cl (ml/min)	139 ± 20	121 ± 20	0.12
C <sub>max</sub> (mg/ml)	42.3 ± 13.1	32.1 ± 6.9	0.06
V <sub>ss</sub> (l)	17 ± 3.6	18.3 ± 2.6	0.20
T <sub>1/2</sub> (h)	108 ± 45	128 ± 32	0.15

AUC, area under the curve; Cl, clearance; MRT, mean retention time; C<sub>max</sub>, maximum concentration; T<sub>max</sub>, time to reach C<sub>max</sub>; V<sub>ss</sub>, volume distribution at steady state; T<sub>1/2</sub><sup>β</sup>, β half-life; T<sub>1/2</sub>, elimination half-life.

**Schedule A.** Dose level 1: two patients had grade IV neutropenia, which was prolonged and dose-limiting in one; both had subsequent dose reductions. There were also two episodes of dose-limiting thrombocytopenia, which occurred in later cycles after the second dose cohort had started. There was also significant anaemia requiring transfusion support (28 units over 10 episodes). Treatment delays affected 10 cycles, representing 36% of those evaluable for delay (i.e. excluding cycle 1). Dose level 2: both patients had dose-limiting neutropenia in the first cycle. One withdrew with progressive disease and the other continued after dose reduction.

**Schedule B.** Dose level 1: there was one dose reduction due to grade IV thrombocytopenia (not dose limiting). No grade IV

neutropenia was documented. Five patients received 10 blood transfusions. Ten treatment delays were necessary (53% of evaluable cycles). Dose level 2: there was one episode of grade IV neutropenia, which was not dose limiting. Grade III thrombocytopenia occurred in three patients but no grade IV toxicity was seen. Five of six patients required blood transfusions. Despite the protocol amendment described above, most cycles (64%) were delayed.

### Non-haematological toxicity

Reported toxicities including nausea, constipation or diarrhoea, and fatigue, were mild (up to grade II). One episode of grade III vomiting was documented with schedule A.

### Antitumour activity

The objective response rate was 14% (three of 21).

**Schedule A.** Five patients had stable disease at the completion of treatment and one with endometrial cancer had a partial response. Median survival was 37 weeks (range 2–109).

**Schedule B.** Three had stable disease, and two had partial responses. Median survival was 20 weeks (range 11–164+); one with adenocarcinoma of unknown primary is alive more than 3 years after enrolment.

### Pharmacokinetics

The results are summarised in Table 2.

**Carboplatin.** Nineteen patients were sampled, but the patient treated at AUC 5 was not included in the analysis. Carboplatin AUCs for both schedules were within 15% of target. Patients treated with schedule A had a slightly higher glomerular filtration rate (GFR) than those receiving schedule B (135 and 98 ml/min, respectively; *P* = 0.04).

**Topotecan.** Dose level 1: 13 patients were analysed. Both open and closed lactone ring topotecan AUCs were greater, and clearance correspondingly lower, with schedule B. Limited pharmacokinetic data did not demonstrate any change in topotecan concentrations (*P* > 0.05) over the 5 days of administration (data not shown). Dose level 2: pharmacokinetics could not be compared as only two patients were treated in schedule A. For schedule B, the higher dose led to increases in both AUC and C<sub>max</sub>.

### Discussion

The difficulty of administering topotecan and platinum together had raised the possibility of a pharmacokinetic interaction [2–4]. In our study, topotecan AUC was higher, and clearance lower, when it was given 1 week after carboplatin rather than during the same week. There was, however, a significant difference in baseline GFR of patients receiving the two schedules. It is unlikely that the observed difference in topotecan clearance was due to the lower GFR in patients receiving schedule B, as topotecan dose adjustments are not

necessary in patients with mild renal impairment [9] let alone in those with filtration rates within normal parameters.

Both schedules of topotecan and carboplatin were active, but with the high incidence of myelosuppression, delays and transfusions, this combination is unlikely to be clinically optimal in its present form. Further studies have addressed the impact of separating platinum and topotecan administration, and have reported less myelosuppression when platinum is given after topotecan rather than the reverse sequence [10, 11].

## Acknowledgements

Supported by the Cancer Research Campaign and SmithKline Beecham Ltd.

## References

1. Johnson R, McCabe F, Yu Y. Combination regimens with topotecan in animal tumor models. *Ann Oncol* 1992; 3 (Suppl 1): 85 (Abstr 107).
2. Miller AA, Hargis JB, Lilenbaum RC et al. Phase I study of topotecan and cisplatin in patients with advanced solid tumors: a cancer and leukemia group B study. *J Clin Oncol* 1994; 12: 2743–2750.
3. Rowinsky EK, Kaufmann SH, Baker SD et al. Sequences of topotecan and cisplatin: phase I, pharmacologic, and *in vitro* studies to examine sequence dependence. *J Clin Oncol* 1996; 14: 3074–3084.
4. Raymond E, Burris HA, Rowinsky EK et al. Phase I study of daily times five topotecan and single injection of cisplatin in patients with previously untreated non-small-cell lung carcinoma. *Ann Oncol* 1997; 8: 1003–1008.
5. Calvert AH, Newell DR, Gumbrell LA et al. Carboplatin dosage: prospective evaluation of a simple formula based on renal function. *J Clin Oncol* 1989; 7: 1748–1756.
6. Harland SJ, Newell DR, Siddik ZH et al. Pharmacokinetics of cis-diamine-1,1-cyclobutane dicarboxylate platinum(II) in patients with normal and impaired renal function. *Cancer Res* 1984; 44: 1693–1697.
7. van Warmerdam LJ, Verweij J, Schellens JH et al. Pharmacokinetics and pharmacodynamics of topotecan administered daily for 5 days every 3 weeks. *Cancer Chemother Pharmacol* 1995; 35: 237–245.
8. Loos W, Stoter G, Verweij J, Schellens JH. Sensitive high-performance liquid chromatographic fluorescence assay for the quantitation of topotecan (SKF 104864-A) and its lactone ring-opened product (hydroxy acid) in human plasma and urine. *J Chromatogr B Biomed Appl* 1996; 678: 309–315.
9. O'Reilly S, Rowinsky E, Slichenmyer W et al. Phase I and pharmacologic study of topotecan in patients with impaired renal function. *J Clin Oncol* 1996; 14: 3062–3073.
10. Thodtmann R, Kemerich M, Depenbrock H et al. A clinical phase I trial of topotecan in combination with carboplatin in patients with advanced solid tumors. *Ann Oncol* 1998; 9 (Suppl 2): 69 (Abstr 263).
11. Bowman A, Rye T, Ross G et al. Reverse schedule topotecan and carboplatin in relapsed ovarian cancer: A phase I/II dose-ranging study. *Eur J Cancer* 1999; 35 (Suppl 4): 232 (Abstr 914).