Duration: escalation study of oral etoposide with carboplatin in patients with varied solid tumors

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Prolonged fractionated oral administration of etoposide may present a theoretical advantage over intravenous administration of the bolus. This phase I trial was carried out to determine the recommended duration of oral etoposide in combination with a fixed dose of carboplatin. Nineteen patients with varied solid tumors, who were not candidates for standard chemotherapy, were administered an escalating duration (6, 9 or 12 consecutive days) of oral etoposide (a 25 mg capsule three times daily) combined with carboplatin AUC5 administered on day 1, by a 30 min intravenous infusion, to define the maximum tolerated dose on the basis of the acute toxicities that were reported. Etoposide was started on day 2; the cycles repeated every 28 days until disease progression or toxicity. Pharmacokinetics was carried out during the two first cycles. The maximum tolerated dose was determined to be the 12-day treatment level, with two cases of grade 4 neutropenia, grade 3 anemia and thrombocytopenia. As no severe toxicity occurred with the 9-day treatment level and in an attempt to explore an optimal combination, a new 10-day treatment plan was studied in three patients. As one patient presented dose-limiting toxicity at that level, five additional patients were included to establish the recommended regimen. Nonhematological toxicities among all patients were moderate, consisting of grade 2 nausea and asthenia. No treatment-related death occurred. Objective responses were observed in four patients and stabilization in three patients. Pharmacokinetics highlighted no interaction between etoposide and carboplatin. Fractionated oral etoposide (3 × 25 mg/day) for 10 days in combination with carboplatin AUC 5 presents acceptable toxicity and efficacy. The main toxicity remains hematological. *Anti-Cancer Drugs* 21:958–962 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Associations of platin compounds and etoposide are a standard regimen in the treatment of many malignancies such as small cell lung cancer, non-small cell lung cancer, germ cell cancer, and endocrine cancers [1–4]. This association could decline through several variations in terms of dosages, schedules, exposure duration, sequences, types of platins with variable toxicity profiles. For instance, carboplatin shows less nephrotoxicity, neurotoxicity, ototoxicity, and emesis than cisplatin [5–8]. In contrast, bone marrow suppression, especially with thrombocytopenia, is more marked [5–8]. Etoposide is a semisynthetic derivative of podophyllotoxin with the ability to inhibit topoisomerase II [9] and is highly schedule-dependent. Its prolonged administration may enhance its effectiveness against resistant tumors [10–13]. Interestingly, the use of oral etoposide allows prolonged administration without the need for repeated or continuous venous access. A phase I/II study assessed escalating doses of carboplatin combined with a fixed dose of oral etoposide [14]. Then, a randomized trial observed that intensive intravenous etoposide combined with carboplatin is similar in efficacy but more toxic than oral etoposide and carboplatin [15]. Yet, no study has assessed the optimal duration of oral etoposide associated with a fixed dose of carboplatin. It has been shown earlier that severe toxicity related to oral etoposide is avoided when peak plasma concentrations do not exceed 3–5 mg/l [16]. In addition, C_{peak} (peak plasma concentration) may be greater than 2 or 3 mg/l when patients receive 75 mg once daily in comparison with 25 mg three times daily [17]. Taking into account the fact that the carboplatin area under the curve (AUC) required to achieve activity is well established [18], a new phase I study aimed at defining the recommended duration of oral etoposide (25 mg three times daily) in combination with a fixed dose of carboplatin AUC seems of interest.

Patients and methods

Eligibility

Adult patients (> 18 years) with histologically confirmed solid malignancy, who were not candidates for standard

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chemotherapy, were eligible to participate in this trial. All patients were required to have adequate hematological function, renal function, and liver function, a performance status between 0 and 2, and an expected survival of longer than 3 months. Patients with clinically evident hearing loss or symptomatic peripheral neuropathy were ineligible. Patients with uncontrolled severe heart disease, neutrophil count less than 1.5×10^9/l, platelet count less than 100×10^9/l, or a creatinine clearance less than 30 ml/min were excluded. Patients could have received chemotherapy earlier. The study protocol was approved by the ethics committees and all patients provided signed informed consent.

Treatment plan

The patients were treated with oral etoposide (25 mg capsule three times daily) combined with a fixed dose of carboplatin calculated to achieve an AUC5. Carboplatin was administered on day 1, by a 30 min intravenous infusion. The AUC of carboplatin was determined using the Chatelut formula [19]. Etoposide was started on day 2; the cycles were repeated every 28 days until disease progression or toxicity. Etoposide duration was planned to be prolonged from 6, 9, 12, 15, and 18 consecutive days and adapted based on the occurrence of severe toxicity. Pharmacokinetics was performed during the two first cycles. A minimum of three patients were entered per etoposide duration level. Dose escalation was not allowed.

The patients were premedicated with an antiemetic treatment including 5-hydroxytryptamine-3 receptor antagonists with corticosteroid sometimes associated with antiemetic agents of a lower therapeutic index. The use of granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor was not allowed as a primary prophylaxis.

Toxicities were graded according to common toxicity criteria [20]. A complete blood cell count was carried out weekly. The maximum tolerated dose (MTD) was defined as one dose level below the level at which two of three patients developed a dose-limiting toxicity (DLT) such as grade 4 leukopenia and neutropenia lasting for more than 7 days, febrile neutropenia, prolonged neutrophil recovery at 28 days while receiving granulocyte colony-stimulating factor, or grade ≥ 3 anemia or thrombocytopenia, or grade ≥ 3 nonhematological (except for vomiting and alopecia) toxicity. A dose escalation to the next duration level was made if no DLT was noted in a cohort of a minimum of three patients and if DLT was seen in one patient, the cohort was expanded to six patients, with the MTD reached if two or more patients experienced a DLT. Then the recommended dose duration (RD) was defined as the longer level at which less than 33% of the patients experienced a DLT. The activity and the safety profile of this combination were assessed with objective response rate, according to Response Evaluation Criteria In Solid Tumors guidelines, duration of response, and time to progression.

Pharmacokinetic evaluation

For carboplatin pharmacokinetic parameters evaluation, blood samples were taken predose, then 0.5, 1, 2, 4, 8, and 24 h after intravenous administration. The timing for etoposide sampling was the following: predose, then 0.5, 1, 2, 3, 6, and 8 h after the initial administration. As the etoposide administration began on day 2 of the first cycle of treatment, the samples intended for the pharmacokinetic study of carboplatin without etoposide were taken on day 1 of this cycle. The samples for the etoposide study were taken 7 days later (at steady state). The samples intended for the pharmacokinetic study of the carboplatin–etoposide interaction were taken on day 1 of the second cycle of treatment. The samples were immediately centrifuged and underwent an ultrafiltration to separate the ultrafiltered (Uf) and total platin (Pt) fractions. The Pt in both fractions was measured using an inductively coupled plasma mass spectrometry method as described earlier [21]. Briefly, using a Hewlett Packard (Les Ulis, France) model 4500 inductively coupled plasma mass spectrometry and bismuth as an internal standard, the calibration curves for Pt were prepared in serum obtained from healthy volunteers and covers the concentration range of 0–1000 µg/l. The samples were prepared by diluting 50 µl of serum with 4950 µl of diluent containing 1% nitric acid and 10 µg/l of bismuth (100-fold dilutions). The limit of detection was 0.01 µg/l, the lower limit of quantification was 0.2 µg/l. The calibration curves exhibited good linearity over the working concentration range of 0–1000 µg/l. Recovery of Pt added to the serum was close to 100% at concentrations of 20 and 200 µg/l. Within-run and between-run coefficients of variation were less than 5% for both the concentrations studied.

Etoposide measurement was done using the high-pressure liquid chromatography–ultraviolet method [22]. Briefly, after an extraction with tert-butyl methyl ether, the samples with an internal standard (phenacetin) are dried and dissolved with a mobile phase (phosphate buffer, 0.01 mol/l, pH = 3.2; acetonitrile; methanol; 60 : 10 : 30 v/v). The samples were separated using an OmniSpher C18 column (150×4.6 mm – 5 µm/Varian, Palo Alto, California, USA) with a detection of 278 nm. Using this method, the limit of detection was 15 µg/l, and the lower limit of quantification was 25 µg/l.

For each patient, AUC was calculated using a trapezoidal method. The AUCs and the values of the maximal concentration (C_{max}) were analyzed and compared using a paired *t*-test.

Results

Patient characteristics

A total of 19 patients with various malignancies entered this study. All patients received one or more cycles

(maximum six cycles). The median age of the patients was 57.2 years (from 42 to 77 years old). The Eastern Cooperative Oncology Group performance status was 0 (five patients), 1 (10 patients) and 2 (four patients). This population was heavily pretreated: surgery (12 patients), radiation therapy (10 patients), hormonal therapy (five patients), adjuvant chemotherapy (seven patients), and metastatic chemotherapy (17 patients). Patient characteristics are summarized in Table 1.

Toxicity

The first cohort of five patients was entered at the first level (oral etoposide 75 mg/d for 6 days) and no DLT was observed. The next cohort of three patients was entered at the second level (oral etoposide 75 mg/d for 9 days) without DLT. A subsequent cohort of three patients was treated at the third level (oral etoposide 75 mg/d for 12 days and two DLT grade 4 febrile neutropenia and grade 3 anemia and thrombocytopenia lasting more than 7 days) were observed in three patients. Then it can be stated that the MTD was reached at this third level. As no DLT occurred at the second level, a new level of duration fixed at 10 days was studied. One DLT occurred (grade 3 thrombocytopenia) among the first three patients. This group was defined as the RD of oral etoposide and was expanded to a total of eight patients without another DLT.

All patients were evaluated for toxicity. At the RD, the most common was the hematological toxicity as shown in Table 2. Febrile neutropenia, grade 3 thrombocytopenia and grade 4 infection with hemoptysia were observed in one patient with 12 days of etoposide. Nonhematological toxicity was infrequent and occurred rarely in our patients as shown in Table 2.

Table 1 Patients characteristics

	Number of patient ($n=19$)
Female	10
Male	9
Performance status (ECOG)	
0	5
1	10
2	4
Type of tumor	
Breast	2
Prostate	3
Head and neck	2
Ovary/endometrium	3
Esophagus/stomach	2
Thyroid	2
Pancreas	3
Sarcoma	2
Earlier treatment	
Surgery	12
Radiation therapy	10
Hormonal therapy	5
Chemotherapy adjuvant	7
Chemotherapy metastatic	17

ECOG, Eastern Cooperative Oncology Group.

Pharmacokinetic assessments were available for 14 patients

Carboplatin pharmacokinetic parameters

The evolution of the concentrations of both total and Uf Pt is illustrated Fig. 1a and b, respectively. These figures clearly showed that there was no difference between the first (circles – without etoposide) and the second cycles (squares – with etoposide). The values of the pharmacokinetic (PK) parameters for each cycle are shown in Table 3. None of these parameters showed a significant difference between the PK parameters of Pt in the presence or absence of etoposide.

Etoposide pharmacokinetic parameters

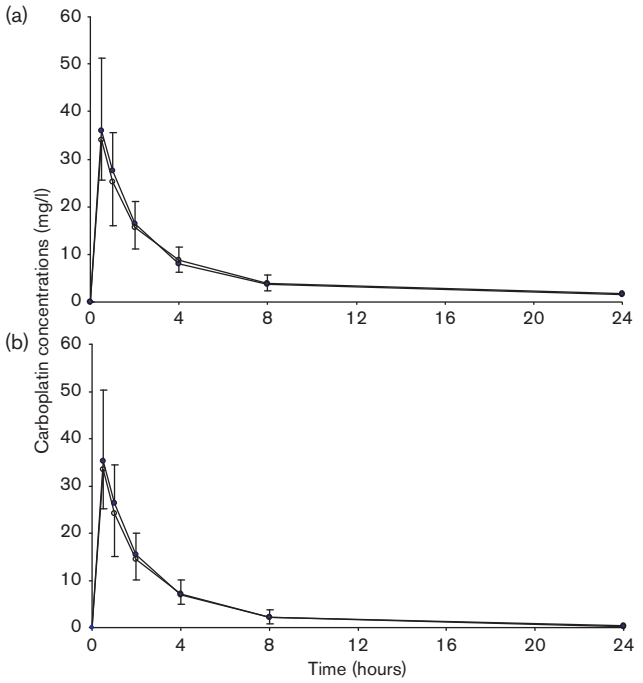
The evolution of the concentrations in time with etoposide concentrations is shown in Fig. 2. The mean

Table 2 Toxicity parameters

	Duration level							
	1st level = 6 days		2nd level = 9 days		3rd level = 12 days		4th level = 10 days	
	Grade 3–4	All grade	Grade 3–4	All grade	Grade 3–4	All grade	Grade 3–4	All grade
Nonhematological								
Asthenia/fatigue	0	3	0	1	0	2	0	5
Diarrhea	0	0	0	0	0	0	0	0
Vomiting	0	1	0	2	0	1	0	2
Stomatitis	0	1	0	1	0	2	0	3
Alopecia	0	2	0	0	0	0	0	2
Infection	0	0	0	1	1	2	0	1
Paresthesia	0	0	0	0	0	0	0	0
Hepatic cytolysis	0	0	0	0	0	0	0	0
Biological cholestasis	0	1	0	0	0	1	0	1
Hematological								
Neutropenia	1	2	0	2	2	3	2	3
Febrile neutropenia	0	x	0	x	1	x	0	x
Anemia	1	4	0	2	1	3	0	6
Thrombocytopenia	0	3	0	0	1	2	1	2

DLTs observed were mainly hematological. Infrequent nonhematological toxicity.
DLT, dose limitant toxicity.

Fig. 1



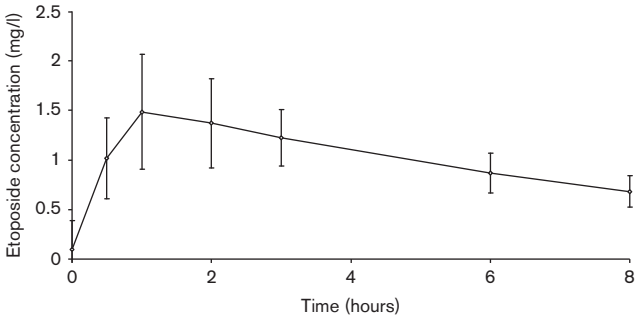
Carboplatin pharmacokinetic: evolution with time of the concentration of total [black symbols – (a)] and ultrafiltered [open symbols – (b)] obtained at first cycle (circles – without etoposide) and the second cycle (squares – with etoposide). The results are expressed as the mean ± standard deviation of 14 patients.

Table 3 Carboplatin pharmacokinetic parameters

	AUC		C_{max}	
	Cycle 1	Cycle 2	Cycle 1	Cycle 2
Ultrafiltered	6.38 ± 2.02	6.27 ± 1.45	37.44 ± 12.38	34.77 ± 9.04
Total	8.11 ± 2.56	7.48 ± 2.84	38.23 ± 12.55	35.41 ± 9.08

AUC, area under the curve.

Fig. 2



Etoposide pharmacokinetic: evolution with time of the concentration of etoposide obtained after the administration of 25 mg per os. The results are expressed as the mean ± standard deviation of 14 patients.

8-h AUC was 8.70 ± 2.15 mg h/l, the mean C_{max} was of 1.66 ± 0.50 mg/l occurred at 1.36 ± 0.63 h. The mean concentration (C_{mean}) was 1.09 ± 0.27 mg/l.

Response and survival

Four patients (21%) with breast cancer, thyroid cancer, and ovarian cancer have shown a complete/partial response, respectively. Three patients (15.7%) have shown stable disease for a total of 36.7% of the patients with a clinical benefit. The median time to progression was 2.9 months. The median survival time was 7.3 months.

Discussion

Optimizing the drug schedule and obtaining efficient concentrations to have maximal antitumoral activity with acceptable toxicities are the goals of phase I trials involving two drug regimens [23].

Evidence of efficiency of the carboplatin and etoposide association has prompted the development of therapeutic strategies to modulate their administration and thus their activity. The combination of carboplatin with an oral compound avoids the need for repeated or continuous venous access and therefore allows a more ambulatory schedule. Optimal exposure to carboplatin is related to efficacy and seems to be well established. It is of interest to fix the carboplatin dosage and to study the variation of oral etoposide exposure duration.

The results obtained with carboplatin PK parameters clearly showed that the presence of etoposide did not modify the Pt pharmacokinetics. This was observed both with Uf and total Pt. This is an interesting point as the other studies focused mainly on the effects of carboplatin on the etoposide pharmacokinetic. With regard to the etoposide concentrations, the C_{mean} was similar to other published studies: 1.10 ± 0.30, 1.40 ± 0.30 for the studies by Minami *et al.* [24] and Ando *et al.* [25]. In this study, the observed C_{mean} was 1.09 ± 0.27 mg/l.

It seems that the interactions between carboplatin and etoposide are mainly about the elimination of etoposide [26]. However, in an earlier study, the doses of both compounds were high. When the doses are lower, the interaction seems weak, or even nonexistent [27,28]. In this study, the administered doses were not high and no interaction between compounds could be observed. The increase in cytotoxicity could be thus more ascribed to the increase in the length of treatment by etoposide than to the administered doses.

This study observed DLT (febrile neutropenia and thrombocytopenia) in two patients under 12 days of oral etoposide. As DLT did not occur while the patients received 9 days of oral etoposide, a search for an optimal duration between 9 and 12 days was conducted. The

recommended duration seems to be 10 days of exposure duration of oral etoposide (25 mg three times daily) with a fixed dose of carboplatin targeted to AUC 5. Toxicity is limited and the quality of life is acceptable. Taking into account that preliminary studies might indicate that prolonged exposure of etoposide was related to higher activity with the ability to come over several mechanisms of resistance, this prolonged exposure to 10 days of etoposide could be of interest. The administration of carboplatin and oral etoposide according to this study seems an interesting option and warrants a comparison with the standard platin-etoposide regimens.

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References

1 Evans WK, Shepherd FA, Feld R, Osoba D, Dang P, Deboer G. VP-16 and cisplatin as first-line therapy for small-cell lung cancer. *J Clin Oncol* 1985; **3**:1471–1477.
2 Roth BJ, Johnson DH, Einhorn LH, Schacter LP, Cherng NC, Cohen HJ, *et al.* Randomized study of cyclophosphamide, doxorubicin, and vincristine versus etoposide and cisplatin versus alternation of these two regimens in extensive small-cell lung cancer: a phase III trial of the Southeastern Cancer Study Group. *J Clin Oncol* 1992; **10**:282–291.
3 Arriagada R, Bergman B, Dunant A, Le Chevalier T, Pignon JP, Vansteenkiste J; International Adjuvant Lung Cancer Trial Collaborative Group. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. *N Engl J Med* 2004; **350**:351–360.
4 Xiao H, Mazumdar M, Bajorin DF, Sarosdy M, Vlamis V, Spicer J, *et al.* Long-term follow-up of patients with good-risk germ cell tumors treated with etoposide and cisplatin. *J Clin Oncol* 1997; **15**:2553–2558.
5 Harland SJ, Newell DR, Siddik ZH, Chadwick R, Calvert AH, Harrap KR. Pharmacokinetics of cis-diammine-1,1-cyclobutane dicarboxylate platinum(II) in patients with normal and impaired renal function. *Cancer Res* 1984; **44**:1693–1697.
6 Evans BD, Raju KS, Calvert AH, Harland SJ, Wiltshaw E. Phase II study of JM8, a new platinum analog, in advanced ovarian carcinoma. *Cancer Treat Rep* 1983; **67**:997–1000.
7 Calvert AH, Harland SJ, Newell DR, Siddik ZH, Jones AC, McElwain TJ, *et al.* Early clinical studies with cis-diammine-1,1-cyclobutane dicarboxylate platinum II. *Cancer Chemother Pharmacol* 1982; **9**:140–147.
8 Egorin MJ, Van Echo DA, Tipping SJ, Olman EA, Whitacre MY, Thompson BW, Aisner J. Pharmacokinetics and dosage reduction of cis-diammine(1,1-cyclobutanedicarboxylato)platinum in patients with impaired renal function. *Cancer Res* 1984; **44**:5432–5438.
9 Fleming RA, Miller AA, Stewart CF. Etoposide: an update. *Clin Pharm* 1989; **8**:274–293.
10 Clark PI, Slevin ML, Joel SP, Osborne RJ, Talbot DI, Johnson PWM, *et al.* A randomized trial of two etoposide schedules in small-cell lung cancer: the influence of pharmacokinetics on efficacy and toxicity. *J Clin Oncol* 1994; **12**:1427–1435.
11 Waits TM, Johnson DH, Hainsworth JD, Hande KR, Thomas M, Greco FA. Prolonged administration of oral etoposide in non-small-cell lung cancer: a phase II trial. *J Clin Oncol* 1992; **10**:292–296.
12 Hainsworth JD, Johnson DH, Frazier SR, Greco FA. Chronic daily administration of oral etoposide: a phase I trial. *J Clin Oncol* 1989; **7**:396–401.
13 Johnson DH, Greco FA, Strupp J, Hande KR Hainsworth JD. Prolonged administration of oral etoposide in patients with relapsed or refractory small-cell lung cancer: a phase II trial. *J Clin Oncol* 1990; **8**: 1613–1617.
14 Frasci G, Perillo G, Comella G, Comella P, Polverino M, Menzella G, Persico G. Phase I/II study of carboplatin and oral etoposide with colony stimulating factor in advanced NSCLC. *Cancer* 1995; **75**: 1578–1585.
15 Jeremic B, Shibamoto Y, Milicic B, Milisavljevic S, Nikolic N, Dagovic A, *et al.* Prolonged oral versus high-dose intravenous etoposide in combination with carboplatin for stage IV non-small-cell lung cancer (NSCLC): a randomized trial. *Lung Cancer* 1999; **25**:207–214.
16 Toffoli G, Corona G, Basso B, Boiocchi M. Pharmacokinetic optimisation of treatment with oral etoposide. *Clin Pharmacokinet* 2004; **43**:441–466.
17 Aydiner A, Koyuncu H, Tas F, Topuz E, Disci R. Crossover clinical study comparing the pharmacokinetics of etoposide (75 mg) administered as 25-mg capsules three times a day versus once a day. *Int J Clin Pharmacol Res* 2000; **20**:21–30.
18 Chatelut E, Pivot X, Otto J, Chevreau C, Thyss A, Renée N, *et al.* A limited sampling strategy for determining carboplatin AUC and monitoring drug dosage. *Eur J Cancer* 2000; **36**:264–269.
19 Chatelut E, Canal P, Brunner V, Chevreau C, Pujol A, Boneu A, *et al.* Prediction of carboplatin clearance from standard morphological and biological patient characteristics. *J Natl Cancer Inst* 1995; **87**:573–580.
20 Common Terminology Criteria for Adverse Events v2.0. *http://ctep.cancer.gov/reporting/ctc.html*.
21 Royer B, Guardiola E, Polycarpe E, Hoizey G, Delroeux D, Combe M, *et al.* Serum and intraperitoneal pharmacokinetics of cisplatin within intraoperative intraperitoneal chemotherapy: influence of protein binding. *Anticancer Drugs* 2005; **16**:1009–1016.
22 Shirazi FH, Bahrami G, Stewart DJ, Tomiak E, Delorme F, Noel D, Goel R. A rapid reversed phase high performance liquid chromatographic method for determination of etoposide (VP-16) in human plasma. *J Pharm Biomed Anal* 2001; **25**:353–356.
23 Van Kesteren C, Mathot RA, Beijnen JH, Schellens JH. Pharmacokinetic-pharmacodynamic guided trial design in oncology. *Invest New Drugs* 2003; **21**:225–241.
24 Minami H, Ando Y, Sakai S, Shimokata K. Clinical and pharmacologic analysis of hyperfractionated daily oral etoposide. *J Clin Oncol* 1995; **13**:191–199.
25 Ando M, Minami H, Ando Y, Sakai S, Shimono Y, Sugiura S, *et al.* Pharmacological analysis of etoposide in elderly patients with lung cancer. *Clin Cancer Res* 1999; **5**:1690–1695.
26 Rodman JH, Murry DJ, Madden T, Santana VM. Altered etoposide pharmacokinetics and time to engraftment in pediatric patients undergoing autologous bone marrow transplantation. *J Clin Oncol* 1994; **12**:2390–2397.
27 Thomas HD, Porter DJ, Bartelink I, Nobbs JR, Cole M, Elliott S, *et al.* Randomized cross-over clinical trial to study potential pharmacokinetic interactions between cisplatin or carboplatin and etoposide. *Br J Clin Pharmacol* 2002 ; **53**:83–91.
28 Newell DR, Eeles RA, Gumbrell LA, Boxall FE, Horwich A, Calvert AH. Carboplatin and etoposide pharmacokinetics in patients with testicular teratoma. *Cancer Chemother Pharmacol* 1989; **23**:367–372.