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ORIGINAL ARTICLE

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A randomized cross-over trial to determine the effect of Cremophor EL on the pharmacodynamics and pharmacokinetics of carboplatin chemotherapy

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Abstract *Purpose*: Paclitaxel, when combined with carboplatin, exhibits a platelet-sparing effect. Paclitaxel is formulated in Cremophor EL (CrEL), which has been shown in preclinical models to reduce haematological toxicity from radiotherapy and chemotherapy. We sought to determine the effect of a 3-h infusion of 20 ml/m^2 (equivalent to 175 mg/m^2 paclitaxel) CrEL on myelosuppression following carboplatin chemotherapy, and the effect of CrEL on carboplatin pharmacokinetics. *Methods*: A total of 16 patients with locally advanced or metastatic cancer were randomized to receive either CrEL or saline over 3 h prior to carboplatin (area under the curve, AUC, 5–7). Each patient was subsequently crossed over to the other treatment. Blood samples were collected at selected time-points for estimation of platinum AUC and 24-h platinum levels. Full blood counts were obtained three times per week. *Results*: Of the 16 patients randomized, 15 were evaluable. Myelosuppression was measured by percentage fall at nadir and nadir levels. No significant differences were obtained when comparing CrEL and saline with respect to the above end-points after adjusting for multiple testing. There was no evidence to indicate that CrEL altered the pharmacokinetics of carboplatin. *Conclusion*: CrEL at this dose and schedule does not appear to be a major contributory factor to the platelet-sparing effect of paclitaxel when combined with carboplatin, nor does it alter the pharmacokinetics of carboplatin.

Keywords Cremophor EL · Carboplatin · Pharmacokinetics/dynamics · Platelet sparing · Myelosuppression

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Introduction

Cremophor EL (CrEL) is a polyethoxylated castor oil that is used as an emulsifying agent in the pharmaceutical and food industries. It is used as the vehicle for several water-insoluble pharmaceutical products including paclitaxel, cyclosporine and teniposide. The toxicity of paclitaxel is due in part to the CrEL vehicle [22]. In a phase I study of paclitaxel, Kris et al. [14] reported hypersensitivity reactions with a dose of ≥190 mg/m^2 of paclitaxel which was attributed to the CrEL equivalent to 20 ml/m^2. Each millilitre of paclitaxel solution contains 6 mg paclitaxel, 527 mg of CrEL (50%) and 50% ethanol. When paclitaxel and carboplatin were combined in early clinical trials, an exciting finding was the observation that more carboplatin was required to produce the same degree of thrombocytopenia than when carboplatin was administered alone [2]. No pharmacokinetic interaction between the two drugs has been observed in previous studies [7].

CrEL has been reported to have a myeloprotective effect in preclinical models [3]. CrEL reduces the haematological toxicity following total body irradiation in

mice. When CrEL was administered prior to near-lethal irradiation doses, the bone marrow regenerative capacity was protected resulting in reduction of post-radiation myelosuppression and long-term survival of the treated mice, and upregulation of B cells, neutrophil expression and macrophage expression was found in the bone marrow of these mice. These were possibly stimulated by cytokines such as histamine triggered by the administration of CrEL [6]. High circulating platelet levels have been recorded in dogs after prolonged infusion of large doses of CrEL [6]. de Vos et al. speculated that the CrEL vehicle contributed to the reduced cisplatin myelotoxicity by altered adduct formation with the critical structures of bone marrow cells [25]. In a panel of in vitro leucocyte cell lines, CrEL in combination with cisplatin has been shown to inhibit DNA adduct formation and leucocyte intracellular cisplatin accumulation by up to 42% compared with cisplatin alone. CrEL's modulatory effects were only seen in haematopoietic cell lines and not in tumour cells. In tumour-bearing mice, this same combination was also seen to significantly reduce haematological toxicity by reducing the uptake of cellular accumulation of cisplatin in the bone marrow [1]. Carboplatin has been found to produce similar adducts to cisplatin in vivo [4].

Our aim in this study was to determine if the paclitaxel vehicle was responsible for the previously observed protection against carboplatin-induced myelosuppression, particularly thrombocytopenia, and to investigate the effect of the CrEL infusion on the pharmacokinetics of carboplatin. The dose and schedule of CrEL were chosen to be equivalent to that delivered in a standard dose of 175 mg/m^2 of paclitaxel infused over 3 h.

Patients and methods

Patients

Eligibility criteria included histologically confirmed locally advanced or metastatic cancer, with up to three prior chemotherapy regimens. Prior radiotherapy was not an exclusion criterion, but had to be completed at least 4 weeks prior to study entry. Radiotherapy could not have been delivered to more than 25% of marrow-bearing areas. Patients were required to have a malignancy in which carboplatin has known activity.

Patients were required to be 18 years or over, not pregnant, with a performance status of 0–3 according to the Eastern Cooperative Oncology Group criteria, and adequate baseline values of haematology (absolute neutrophil count of $\geq 2.0\times10^9$ l^{-1}, a platelet count $\geq 100\times10^9$ l^{-1}, and a haemoglobin $\geq$10 g/dl), renal function (glomerular filtration rate: GFR, $\geq$40 ml/min, as measured by Tc^{99m}DTPA clearance uncorrected for surface area), and hepatic function (serum bilirubin $\leq$ 17 μmol/l, AST/ALT not more than five times the upper limit of normal). Life expectancy was at least 3 months. Written informed consent was obtained from each individual, and the protocol was approved by the institutional ethics committee.

Study design

Patients were randomised to one of two groups. The study design was an open-label 2×2 randomized cross-over design. The "CrEL first" arm received CrEL prior to the first cycle of carboplatin and saline control prior to the second cycle. The "saline first" arm received saline control prior to the first cycle of chemotherapy, and CrEL prior to the second cycle. In order to prevent hypersensitivity reactions to CrEL and to minimize differences between the CrEL and saline control cycles due to such reactions, patients were given dexamethasone 8 mg, promethazine 25 mg, and ranitidine 50 mg all intravenously 30 min prior to starting the CrEL infusion and the saline control.

Treatment

Carboplatin (Delta West, Perth, Australia) was given as a 1-h infusion commencing immediately after the CrEL or the saline control infusion. The dose of carboplatin was calculated to target an AUC of 5–7 mg/ml min according to the formula of Calvert et al. [5]: total dose (mg) = target AUC (GFR + 25). The glomerular filtration rate was measured by Tc^{99m}DTPA clearance [16]. The starting dose of carboplatin was determined by the treating physician (AUC in the range 5–7), with the intention that the dose would be the same for the first two cycles. Cycles were to be repeated every 28 days. CrEL (Cremophor 25% in saline from DBL, a subsidiary of Faulding Healthcare) was administered as a 3-h intravenous infusion in 1000 ml 0.9% saline. The dose was 20 ml/m^2. Infusions were to be mixed as closely as possible to the start of each infusion. For the saline control, 1000 ml 0.9% saline was infused over 3 h.

Carboplatin (platinum) pharmacokinetic analysis

Pharmacokinetic studies of platinum (Pt) from carboplatin were performed on a subset of patients (six blood, 11 urine) during their two treatment cycles. In six patients, blood was sampled prior to the start, 30 min into carboplatin infusion, at the end of the infusion and at selected time-points up to 24 h (15, 30, 60, 90 min, 2, 4, 6, 9, 12, 18 and 24 h after infusion) for both cycles. Following centrifugation, plasma samples were stored at −70°C until ultrafiltrates were prepared using Centristart (Sartorius, Melbourne, Australia) ultrafiltration tubes. In a further two patients, only a 24-h blood sample was available for Pt analysis. Urine was collected for 24 h from ten patients, the volume was measured, and an aliquot frozen until analysis. Platinum concentrations were measured using validated graphite furnace

atomic absorption spectrophotometry assay using a SpectrAA600 instrument (Varian, Australia) [16]. Within-day and between-day variation for accuracy and precision were 15%. The limit of quantitation (variation $<20\%$) was 0.19 μM in plasma and ultrafiltrate, and 1.92 μM in urine. Pharmacokinetic parameters were calculated for ultrafilterable (free) Pt using Siphar/Win Version 1.2b software (SIMED) on a model-independent basis using at least four terminal elimination time points to estimate terminal elimination half-life. $AUC_{0-24\ h}$ was calculated using the trapezoidal rule.

Pharmacodynamic analysis

Pharmacodynamic relationships between the treatment groups (with and without CrEL) were evaluated by generating scatter plots of the percentage decrease for absolute neutrophil and platelet counts and haemoglobin at the nadir in courses one and two vs (1) 24-h total platinum concentrations (from eight patients), and (2) ultrafilterable platinum $AUC_{0-24\ h}$ for six of the eight patients who had a pharmacokinetic profile done. The percentage decrease was defined as follows:

$$\frac{100\% \times (\mathrm{Count_{baseline}} - \mathrm{Count_{nadir}})}{\mathrm{Count_{baseline}}}$$

Linear regression was used to fit the data to a linear model. Nonlinear least-squares regression was used to fit the data to the sigmoid E_{max} pharmacological response model, as described by modified Hill equations [26]. For the sigmoid E_{max} model:

$$\text{Percentage decrease} = \frac{E_{\max} \times C^s}{C^s + \mathrm{EC}_{50}^s}$$

E_{max} is fixed at 100% decrease in counts, C is the pharmacokinetic parameter, EC_{50} is the value of C that produces 50% of the maximal effect, and s is the Hill coefficient. Both, EC_{50} and s were estimated by nonlinear regression.

Toxicity

The duration of grade 3 or 4 WHO neutropenia, thrombocytopenia and anaemia was measured. Duration was defined as the number of days in a cycle with thrombocytopenia, neutropenia and anaemia at $<50\times10^9\ l^{-1}$, $<1.0\times10^9\ l^{-1}$ and <80 g/l, respectively. Toxicity was also measured by treatment delays, infections and requirements for transfusions.

Statistical methods

The main method of analysis was that for a 2×2 cross-over trial in which patients were given two different treatments in their two cycles of chemotherapy, and the treatment order was randomized [13]. The carry-over effects were tested first since tests for the direct (CrEL) and cycle effects are only appropriate when the carry-over effects from Cremophor and saline are equal. The significance levels of all effects were tested using Student's t-test and because of the small sample size, the nonparametric Pitman permutation test was also used to confirm results. As the conclusions remained the same upon applying the nonparametric test, only the results from the Student's t-test are reported and the results from the nonparametric test are not presented. The analyses were performed using Excel 2000 (Microsoft Corporation) and the StatXact-4 software (Cytel Software Corporation). The pharmacodynamic modelling was performed using GraphPad Prism version 3.02 (GraphPad Software) and Excel 2000.

Results

This was a single-institution trial that accrued 16 patients of whom 15 were included in the final analyses. One patient who was randomized to the CrEL first arm was excluded. This patient received a 25% reduction of carboplatin dose in the second cycle due to grade 4 thrombocytopenia experienced in the first cycle. Patient characteristics are summarized in Table 1.

Effect of CrEL on haematological toxicity of carboplatin

Nadir and percentage decrease in haematological levels

Results of the comparisons between CrEL and saline cycles with respect to the nadir and percentage decrease in haematological levels using an analysis of variance model for 2×2 cross-over studies are presented in Table 2. There was no evidence for a carry-over effect in any of the analyses performed. Although it is of importance to analyse the nadir haematological level, the percentage decrease in haematological level is considered more pharmacologically relevant as it allows for the pretreatment haematological level in each cycle for each patient. None of the tests performed was considered to be significant in view of the multiple number of endpoints tested. Note that the nominally significant result associated with the platelet nadir ($P=0.047$) could well be a chance finding. Overall, there was no evidence to indicate that CrEL was associated with a modulation of either nadir or percentage decrease in haematological levels.

Duration of WHO grade 3 neutropenia, thrombocytopenia and anaemia

No patient had grade 4 haematological toxicity. Grade 3 cytopenias were reported in three patients, all occurring in the saline cycle. Of the three patients, one had both neutropenia and thrombocytopenia in the same cycle. The durations were 7 days for neutropenia (one case), 3 days for thrombocytopenia (two cases), and 1 day for anaemia (one case).

Table 1 Patient characteristics

		"CrEL first" arm	"Saline first" arm	Total
Age	Median	66	56	63
	Range	57–75	41–83	41–83
Sex	Male	1	0	1
	Female	6	8	14
Body surface area (m^2)	Median	1.84	1.84	1.84
	Range	1.46–2.13	1.61–2.40	1.46–2.40
Primary cancer treated	Cervix	1	3	4
	Endometrium	2	2	4
	Ovary	2	3	5
	Adenocarcinoma	2	0	2
Prior chemotherapy		2	4	6
Number of prior regimens	0	5	4	9
	1	0	1	1
	2	1	1	2
	3	0	2	2
	4	1	0	1
GFR (ml/min)	Median	69	72	71
	Range	54–108	59–99	54–108
Carboplatin dosing	AUC 5	2	2	4
	AUC 6	3	3	6
	AUC 7	2	3	5
Platelet count prior cycle 1 ($\times 10^9\ l^{-1}$)	Median	243	261	251
	Range	174–471	199–429	174–471
Haemoglobin prior cycle 1 (g/l)	Median	131	118	125
	Range	115–144	101–142	101–144
White cell count prior cycle 1 ($\times 10^9\ l^{-1}$)	Median	6.3	6.2	6.3
	Range	4.2–12.8	5.0–7.6	4.2–12.8

Table 2 Estimated differences between CrEL and saline cycles with respect to the percentage fall in haematological levels from baseline to nadir and the nadir

				Estimated mean difference (95% CI)	*P* value[a]
Fall in platelet count from baseline to nadir (%)	Cremophor cycle	Mean	49	−1% (−9%, 7%)	0.72
		SD	22		
	Saline cycle	Mean	50		
		SD	24		
Platelet nadir ($\times 10^9\ l^{-1}$)	Cremophor cycle	Mean	151	16 (0.2, 32)	0.047
		SD	80		
	Saline cycle	Mean	134		
		SD	76		
Fall in neutrophil count from baseline to nadir (%)	Cremophor cycle	Mean	40	−4% (−16%, 8%)	0.48
		SD	22		
	Saline cycle	Mean	45		
		SD	20		
Neutrophil nadir ($\times 10^9\ l^{-1}$)	Cremophor cycle	Mean	2.1	0.4 (−0.01, 0.8)	0.057
		SD	1.0		
	Saline cycle	Mean	1.8		
		SD	0.8		
Fall in haemoglobin level from baseline to nadir (%)	Cremophor cycle	Mean	13	0.2% (−3.2%, 3.7%)	0.88
		SD	10		
	Saline cycle	Mean	13		
		SD	8		
Haemoglobin nadir (g/l)	Cremophor cycle	Mean	105	0.3 (−3.2, 3.9)	0.84
		SD	18		
	Saline cycle	Mean	105		
		SD	16		

[a]Analysis based on methodology for 2×2 cross-over studies.

Treatment delays

All treatment delays of cycle 2 were due to low neutrophil counts ($< 2.0\times 10^9\ l^{-1}$) on day 28. The number of patients with low neutrophil counts on day 28 in the CrEL first and saline first arms were four and three, respectively ($P = 0.62$, Fisher exact test).

Infections

There were no infections reported that were possibly or definitely related to the treatment.

Transfusions

Of the 15 patients analysed, 14 did not require transfusions in either cycle. One patient required two units of packed cells in both cycles due to anaemia.

Effect of CrEL on nonhaematological toxicities

For five patients, different grades of nausea and vomiting were reported in the two cycles (higher grade in CrEL cycle for four patients and higher grade in saline cycle for one patient; $P = 0.39$, Cochran–Armitage trend test). Other nonhaematological toxicities reported included lethargy, stomatitis, fatigue, diarrhoea, weight loss, feeling cold and right ankle swelling; each toxicity was reported in no more than two patients.

Hypersensitivity reactions

There were two WHO grade 1 hypersensitivity reactions during the CrEL infusions. The CrEL infusions were continued after a brief interruption in these two patients.

Effect of CrEL on plasma platinum pharmacokinetics following 3-h CrEL

Total plasma Pt and ultrafilterable Pt from 0 to 24 h at all prespecified time points following administration of carboplatin with and without CrEL were obtained for six patients, thus providing data for analysing the 24-h total Pt, AUC, C_{max} free Pt, and half-life free Pt. Data on the total plasma Pt at 24 h were also available from two additional patients who did not have complete Pt data from 0 to 24 h. Hence, a total of eight patients were evaluable for the analysis of 24-h total Pt. Pt urinary excretion to 24 h was obtained from a total of ten patients. The results of the comparisons between CrEL and saline cycles with respect to these pharmacokinetic parameters using an analysis of variance model for 2×2 cross-over studies are presented in Table 3. There was no evidence for a carry-over effect in any of the analyses performed. These data give no evidence to indicate that CrEL altered the pharmacokinetics or the renal excretion of Pt from carboplatin (Table 3), although the lack of significance in the results could have been due to the small sample sizes.

Influence of CrEL on the pharmacokinetics/pharmacodynamics of carboplatin

Pharmacodynamic analysis was performed using ultrafilterable Pt AUC_{0-24} ($n = 6$) and 24-h total platinum ($n = 8$). Haematological measurements were available for all patients. For the percentage change in neutrophil count, platelet count and haemoglobin, in both the CrEL and saline cycles, no pharmacodynamic model adequately described the relationship with the pharmacokinetic variables. The pharmacodynamic models were limited by the small sample size, and hence the parameter estimates were characterised by the wide confidence intervals. A comparison of the pharmacodynamic models for the AUC_{0-24} and the 24-h total Pt for the percentage change in the platelets between cycles with and without CrEL, given the above limitations, was unable to identify a platelet-sparing effect with any certainty (Fig. 1).

Discussion

Since Belani et al. reported that there is an interesting platelet-sparing effect on the dose-limiting toxicity of carboplatin when combined with paclitaxel, the mechanism by which this occurs has not been elucidated [2]. Preclinical work has suggested that the paclitaxel vehicle, CrEL, may play a role. Our aim was to determine if CrEL alone, when administered with carboplatin, could be responsible for the platelet-sparing effect seen when carboplatin is combined with paclitaxel in CrEL. We conducted a randomized cross-over trial to determine the influence of a 3-h infusion of CrEL on myelosuppression after carboplatin chemotherapy. CrEL did not have a significant effect on the percentage fall in platelets, neutrophils or haemoglobin. There was a small but statistically significant effect on the platelet nadir. When adjusted for multiple analyses, however, this was no longer significant. Although 14 of the 15 patients analysed were female, it is unlikely the imbalance in gender caused bias in the results reported. We did not observe with this study dose and schedule of CrEL any significant pharmacokinetic interaction with carboplatin. This is consistent with the findings of other studies that have also demonstrated no alteration in pharmacokinetics with platinum/CrEL combinations [1, 7, 8].

There has been considerable interest in the potential mechanisms of the platelet sparing seen with the paclitaxel and platinum regimens. Earlier research focused on CrEL's ability to potentially reverse P-glycoprotein-associated multidrug resistance (P-gp MDR), a mechanism of paclitaxel resistance in vitro [27, 28]. Paclitaxel infusions of 3 h can result in sustained levels of plasma CrEL concentrations that are sufficient for reversal of P-gp associated MDR in vitro [21]. Subsequently CrEL was shown to have an extremely small volume of distribution, limited to the central plasma compartment [24], and as such it was thought unlikely to play a role in reversing P-gp MDR to paclitaxel in vivo. Recently, however, there has been renewed interest in P-gp-mediated activity. It has been postulated that the activity of P-gp MDR gene-encoded membrane-bound transport protein plays an important role in megakaryocyte cell resistance to paclitaxel and this may be partly responsible for the platelet-sparing effect [18]. Significantly less decline in growth in megakaryocyte than in granulocyte/macrophage and erythroid colonies from $CD34^+$ cells

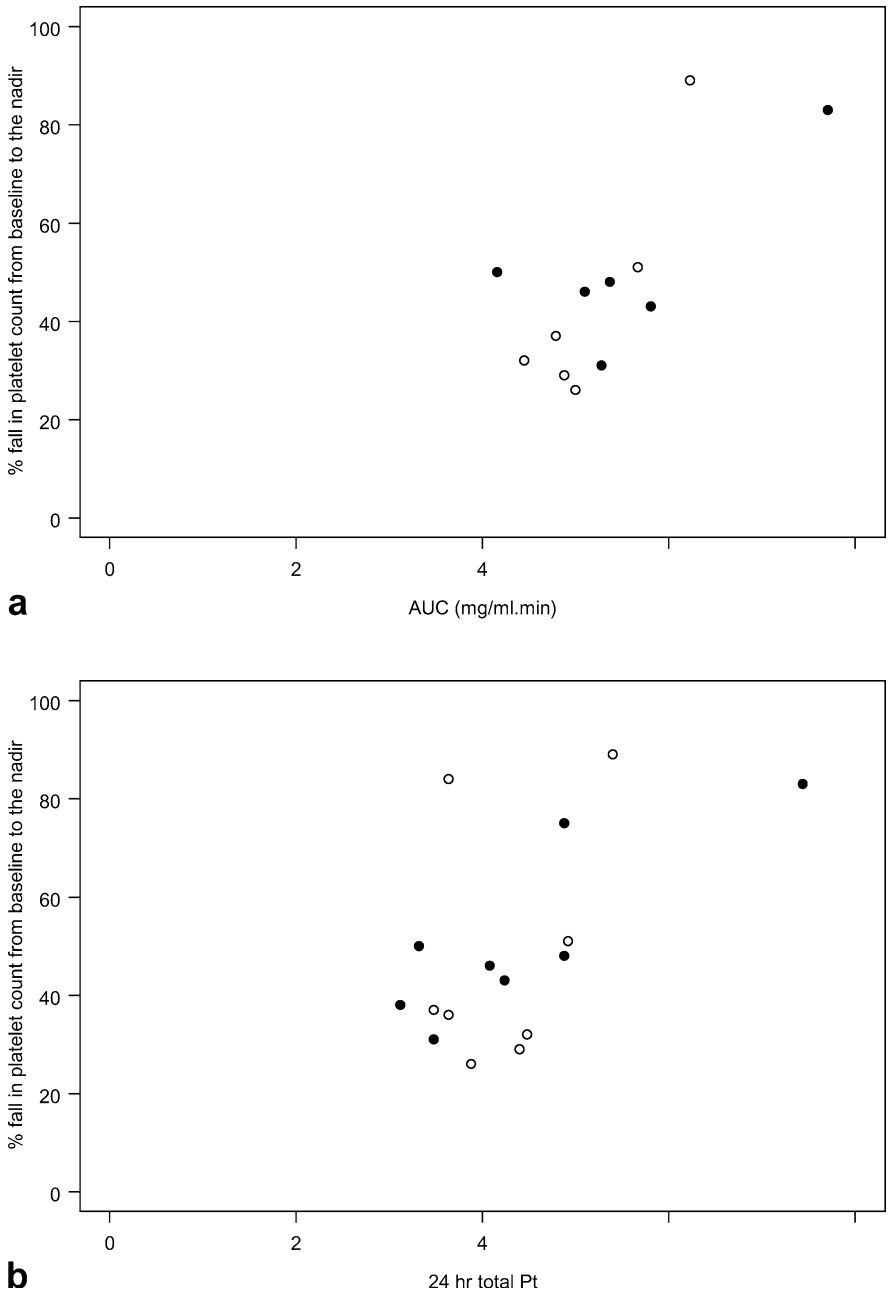

Fig. 1 **a** Percentage fall in platelet count from baseline to the nadir vs carboplatin AUC_{0-24} for courses with CrEL (*filled circles*) and without CrEL (*open circles*). **b** Percentage fall in platelet count from baseline to the nadir vs 24-h total platinum for courses with Cremophor (*filled circles*) and without Cremophor (*open circles*)

collected from patients receiving the paclitaxel and carboplatin combination was observed. Whilst FACS analysis found no difference in P-gp expression in the three different cell lines, exposure to verapamil, a P-gp pump inhibitor, increased the toxicity to the megakaryocyte cells to a level almost the same as that seen in the other cell lines. In this same study, serum thrombopoietin levels were also found to be elevated in 60% of patients.

Any interaction between carboplatin and paclitaxel is likely to occur at the level of the megakaryocyte. Carboplatin and paclitaxel have been studied both alone and in combination in vitro for their antiproliferative effect on the platelet precursor, using the megakaryoblast cell line MEG-01. Using median effect analysis, low doses of paclitaxel and carboplatin had an antagonistic interaction on the growth of MEG-01 cells [10, 11]. In one study [11], the possibility that the interaction occurs between carboplatin and CrEL was investigated. No difference in growth inhibition was observed between MEG-01 cells treated with carboplatin alone and those treated with carboplatin plus CrEL, but a significant interaction occurred between carboplatin and paclitaxel, again suggesting that the CrEL vehicle alone is not responsible for this phenomenon. The results of our study are consistent with those of other smaller clinical studies that have shown a clinically nonsignificant myelosparing effect of CrEL

Table 3 Estimated differences between CrEL and saline cycles with respect to the pharmacokinetics of platinum from carboplatin

				Estimated mean difference (95% CI)	*P* value[a]
24-h total Pt (μM) ($n=8$)	Cremophor cycle	Mean	4.4	0.2 (−0.3, 0.7)	0.35
		SD	1.4		
	Saline cycle	Mean	4.2		
		SD	0.7		
AUC[b] (mg/ml min) ($n=6$)	Cremophor cycle	Mean	5.6	0.4 (−0.2, 1.0)	0.12
		SD	1.2		
	Saline cycle	Mean	5.2		
		SD	0.7		
C_{max} free Pt (μM) ($n=6$)	Cremophor cycle	Mean	84	1.3 (−5.9, 8.4)	0.65
		SD	21		
	Saline cycle	Mean	83		
		SD	18		
$T_{1/2}$ free Pt (h)[c] ($n=6$)	Cremophor cycle	Mean	4.8	−0.1 (−0.5, 0.4)	0.70
		SD	0.5		
	Saline cycle	Mean	4.9		
		SD	0.2		
Percent dose to 24 h in urine ($n=10$)	Cremophor cycle	Mean	61	4.0 (−4.6, 12.6)	0.31
		SD	10		
	Saline cycle	Mean	57		
		SD	10		

[a]Analysis based on methodology for 2×2 cross-over studies.
[b]AUC of carboplatin.
[c]Terminal elimination half-life of platinum.

in combination with cisplatin. In a phase I study, cisplatin (70 mg/m^2 weekly) and oral topotecan (0.45 mg/m^2) were administered with and without CrEL to six patients with recurrent ovarian cancer. CrEL did not impart a significant clinically beneficial myeloprotective effect, despite promising results of a previous study in three patients which showed a small but significant reduction in percent decrease in both leucocyte and platelet parameters with this combination [8, 9]. The authors acknowledged limitations of their studies which involved small numbers of patients, and concurrent use of topotecan, a highly myelotoxic drug, which may have influenced the results. Our trial with its slightly larger numbers and a randomized cross-over design had theoretically greater power to demonstrate an effect of CrEL on carboplatin-induced thrombocytopenia, and was not subject to any confounding interaction with another myelosuppressive agent.

Recently, in one large phase III study of patients with metastatic breast cancer, a possible platelet-sparing effect has been observed with the addition of a taxane to gemcitabine [17]. Other trials using this combination in other cancers have also shown less than expected haematological toxicity [12, 20]. One study, in which the pharmacological relationship between these two drugs was evaluated, showed significant alteration of gemcitabine pharmacokinetics in the presence of paclitaxel [23]. Another study showed no such interaction, but the active metabolite of gemcitabine was increased [15]. A recent multicentre phase III trial comparing paclitaxel, etoposide and carboplatin to carboplatin, etoposide and vincristine in the treatment of small-cell lung cancer showed significantly less severe anaemia, leucopenia and particularly thrombocytopenia in the arm containing paclitaxel [19]. It seems possible that paclitaxel may have a platelet-sparing effect that is not limited to just one chemotherapeutic combination.

In conclusion, this randomized cross-over study demonstrated that this dose and schedule of the paclitaxel vehicle CrEL does not result in a clinically significant decrease in thrombocytopenia, when combined with carboplatin chemotherapy in cancer patients. Our study also confirmed previous findings that CrEL does not alter the pharmacokinetics of carboplatin. Further research is required to determine the mechanism of the favourable platelet-sparing effect observed with paclitaxel combined with particular chemotherapeutic agents.

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