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Iproplatin and Carboplatin Induced Toxicities: Overview of Phase II Clinical Trial Conducted by the EORTC Early Clinical Trials Cooperative Group (ECTG)

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Abstract—*Data of five phase II clinical trials on iproplatin and carboplatin, conducted by the ECTG, have been pooled in order to evaluate the extent of toxicities of these compounds.*

One hundred and seventy patients treated with iproplatin and 65 patients treated with carboplatin were evaluable. Most of them (81%) had been previously treated with chemotherapy. Doses ranged from 180 to 300 mg/m² every 4 weeks for iproplatin, and from 350 to 450 mg/m² every 5 weeks for carboplatin, according to the initial status of the patient. WHO criteria were used to grade toxic effects. Weekly blood counts were performed, and lowest observed counts were analysed by non-parametric methods. Censored data were analysed by actuarial methods.

Thrombocytopenia was the dose-limiting toxicity and was dose related. Leucopenia was less severe. The risk of thrombocytopenia varied largely amongst patients, and could be predicted from the initial platelet count, the initial creatinine level and prior therapy with alkylating agents. The cumulative risk increased with the total dose, but with a decreasing hazard rate, and without additional delay to platelet recovery. Nausea, vomiting and diarrhoea were the most frequently observed non-haematological side-effects, and were more severe with iproplatin than with carboplatin. Peripheral neuropathy was observed in some cases, but could be due to prior treatments. Renal toxicity did not cause major problems.

Our results confirm the findings of the phase I trials: thrombocytopenia is dose-limiting for both drugs, and renal side-effects are negligible. The risk model of thrombocytopenia, consistent with Egorin's model for carboplatin, could serve as a basis for dose adjustment. The feasibility of the scheme could be insufficient for prolonged treatment.

INTRODUCTION

In 1984 and 1985, the ECTG conducted several phase II trials on iproplatin (*cis*-dichloro-*trans*-dihydroxy-bis-isopropylamine platinum IV; CHIP; JM9; NSC 256927) in advanced breast, ovary, head and neck and testes cancer and on carboplatin (*cis*-diamine-1,1-cyclobutane dicarboxylate platinum II; CBDCA; JM8; NSC 241240) in advanced breast and stomach cancer. The activity of both drugs has been reported elsewhere ([1–4] and Vermorken J *et al.*, personal communication).

The aim of the present analysis is to evaluate the extent of side-effects, by pooling data from the different studies. Phase I trials, with both drugs, suggested that thrombocytopenia would be the most frequently encountered side-effect, and the dose-limiting toxicity. This finding was confirmed, and factors increasing the risk of thrombocytopenia were evaluated by multivariate analyses. Several end-points suggesting a dose-cumulative effect were investigated. Non-haematological side-effects were also evaluated and, more specifically, nausea and vomiting, diarrhoea and nephrotoxicity.

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MATERIALS AND METHODS

Between January 1984 and November 1985, 321

Table 1. Patient characteristics (patients included in the analysis)

	Iproplatin				Carboplatin	
	Head and neck	Testis	Ovary	Breast	Breast	Stomach
No. of patients	38	16	96	20	29	36
Age:						
median	57	30	55	55	53	57
min–max	42–78	20–56	33–78	37–65	34–71	31–69
Patients with PS						
0	9	8	19	4	9	4
1	21	4	53	10	10	17
2	8	4	24	6	10	10
3						5
Patients with prior						
Radiotherapy	34	5	16	12	23	1
Chemotherapy	22	16	82	19	29	23
Cisplatin	18	16	70	0	2	3
Aklyl. agents	0	13	78	11	17	2
Anthracyclines	0	3	50	18	27	22
Antimetabol.	21	1	16	15	20	22
Antibiotics	16	16	7	9	13	18
Vinca-alkal.	6	16	1	10	11	0
Podophyllotx.	0	14	1	0	0	1
Hexamethylm.	0	0	30	0	0	0
Alkyl. + Anthr.	0	3	48	10	16	1
Alkyl. + A.meta.	0	1	16	11	14	1

patients were registered in five phase II clinical trials on two different platinum derivatives: a randomized trial of carboplatin vs. iproplatin in advanced breast cancer, a trial of carboplatin in advanced gastric cancer, and three trials on iproplatin in advanced head and neck, ovarian and testicular cancer.

Case records were reviewed by the study coordinators, who excluded 45 cases because of ineligibility (27 cases), improper treatment (five cases), early death not due to toxicity (three cases) or incomplete data (10 cases). Additionally, 41 cases could not be included in the present analysis because weekly blood counts had not been taken (mostly due to institutional policies). A total of 235 cases were included in the analysis, 170 patients on iproplatin and 65 patients on carboplatin.

Patient characteristics are given in Table 1. Performance status (PS) ranged from 0 to 2 (WHO scale), but in the study on gastric cancer a PS of 3 was allowed (five patients). Median age was around 55 years in all studies, except for the patients with testicular cancer who had a median age of 30 years. Most patients had been previously treated with chemotherapy (81%). In the majority of the cases, prior therapy included alkylating agents (51%) and/or anthracyclines (51%). Prior cisplatin had been given to 46% of the patients, in particular those with cancer of the testes, ovary and head and neck.

Both drugs were administered intravenously, iproplatin as a 1 h infusion every 4 weeks, and carboplatin within 15–30 min, every 5 weeks. Iproplatin was given at a dose of 240 mg/m^2 to patients who had a low performance status or had been heavily pretreated (poor risk), and at a dose of 300 mg/m^2 to good risk patients; for carboplatin those figures were 350 and 400 mg/m^2 respectively in stomach cancer. Only patients with breast cancer were treated at a higher dose of 450 mg/m^2. It must be mentioned here that the last patients registered were given lower doses of iproplatin, both in the poor risk group (180 mg/m^2) and in the good risk group (240 mg/m^2), because severe toxicities had been encountered in previous patients.

Patients received a median of two cycles of therapy, ranging from one to nine, according to their response to treatment. Most of the patients treated with more than five cycles belonged to the ovarian cancer trial.

Treatment was postponed for up to 2 weeks if the nadir platelet count was below 130×10^9/l or the nadir leucocyte count below 2×10^9/l. If full recovery was not achieved at that time, doses were reduced to 80% if the platelet count was above 100×10^9/l and the leucocyte count above 2×10^9/l, and to 50% below these limits. Treatment was definitively stopped if the platelet count was below 75×10^9/l or the leucocyte count below 1.5×10^9/l. Doses were also adjusted as a function of the nadir counts at the preceding cycle: 80% of

the dose was given if the nadir platelet count was below 50 × 10^9/l or the nadir leucocyte count below 1.5 × 10^9/l, and doses were reduced to 50% if the nadir platelet count was below 20 × 10^9/l or the nadir leucocyte count below 1 × 10^9/l.

Patients included in the present analysis were followed at least weekly during the treatment. All side-effects were graded according to the WHO toxicity scoring system [5].

Both the median and range of nadir haematological values observed during the first cycle of therapy were computed, and comparisons between subgroups of patients were performed using the Wilcoxon rank test [6].

Risk factors for severe thrombocytopenia (WHO grade 3 or 4: platelet count below 50 × 10^9/l) were evaluated for the first cycle of therapy, using two different methods. The occurrence of severe thrombocytopenia was analysed by a stepdown logistic regression model [7]. The percentage reduction in the platelet count [PRed(Pla)], as defined by Egorin *et al.* [8]* was explored by a linear regression analysis, and our data were compared to the carboplatin results published by Egorin *et al.* [8, 9]. In both analyses, the following variables were investigated as potential risk factors: initial dosage; tumour type and localization of the lesions; age, sex and initial performance status of the patient; initial haematological values, bilirubin and creatinine levels; prior radiotherapy, chemotherapy, the interval since the last drug administration, and the type of drugs previously received (cisplatin, alkylating agents, anthracyclines, antimetabolites, antibiotics, vinca-alkaloids, podophyllotoxins and hexamethylmelamine).

Several end-points suggesting an eventual 'dose-cumulative' effect were studied. As different interpretations could be given to the expression 'dose-cumulative', different methods of analysis have been used.

The cumulative risk of severe thrombocytopenia was estimated as a function of the total dose by the Kaplan–Meier method [10]. Subgroups of patients were compared by the log-rank test [11]. The instantaneous risk (hazard rate) was estimated as a function of the total dose, using Gehan's method [12]. Increase of the hazard rate (but not only of the cumulative risk) would indicate that the cumulated dose previously received (independently of the schedule) increases the risk, even in patients who initially tolerated the treatment.

Nadir leucocyte and platelet counts were compared between successive cycles in the same patient, excluding courses given at reduced doses, or delayed; the non-parametric Wilcoxon pairwise comparison test was used for this purpose. This tests the feasibility of prolonged treatment without dose or schedule adjustment, but only in patients who tolerated the first cycle(s) of therapy.

*PRed(Pla) = 100 × (IPL-NPL)/IPL, where IPL = initial platelet count and NPL = nadir platelet count.

Table 2. Haematological toxicities at 1st cycle

	Iproplatin			Carboplatin		
mg/m²	180	240	300	350	400	450
No. of patients	7	146	17	12	26	27
WBC count (× 10^9/l)						
Nadir value						
Median	4.1	3.7	3.8	4.0	3.5	2.6
Minimum	3.6	0.1	0.9	1.0	0.4	0.8
Maximum	4.9	15.1	8.1	15.4	15.4	7.4
WHO level						
0: >4	4	64	6	6	9	7
1: 3–4	3	36	4	4	9	3
2: 2–3	0	30	5	1	4	10
3: 1–2	0	13	1	0	2	5
4: <1	0	3	1	1	2	2
Platelet count (× 10^9/l)						
Nadir value						
Median	106	95	67	138	75	49
Minimum	40	2	12	60	10	8
Maximum	175	415	480	307	310	201
WHO level						
0: >100	4	70	5	7	11	9
1: 75–100	1	20	3	3	2	2
2: 50–75	1	16	1	2	4	2
3: 25–50	1	23	5	0	4	8
4: <25	0	17	3	0	5	5

Median time to nadir and to recovery were estimated for successive cycles of therapy. As patients could be retreated (with reduced doses) if blood counts were not fully recovered, time to recovery could be censored: therefore, the Kaplan–Meier method was used to estimate the median [10], and the log-rank test [11] to compare successive cycles.

Non-haematological side-effects were reported in contingency tables (the worst WHO level across cycles), and comparisons between subgroups were performed using the chi-square test for trend [13].

RESULTS

1. *First cycle of therapy: myelosuppression*

After the first cycle of drug administration, thrombocytopenia was recorded in 60% of the patients, and at a severe or life-threatening level (WHO grade 3/4) in 31% of the cases. Leucopenia was recorded in 64% of the patients, but only in 13% at a severe or life threatening level.

Table 2 gives the distribution of nadir leucocyte and platelet counts, as well as the medians and ranges, stratified by drug and doses. These data suggest an increase of both leucopenia and thrombocytopenia with increasing doses of therapy. For patients treated with 450 mg/m² of carboplatin,

differences are statistically significant ($P = 0.005$: leucocytes and $P = 0.01$: thrombocytes). For iproplatin, unadjusted comparison of toxicities between dose levels would have been irrelevant, because doses were largely adapted to the patients' initial status. In order to study the dose-effect, a multivariate analysis was performed, which included the different risk factors.

2. *Risk factors of severe thrombocytopenia*

Risk factors were investigated by using a step-down logistic regression model. The dependent variable was the occurrence of severe thrombocytopenia during the first cycle of therapy. The analysis was carried out separately for the two drugs. For iproplatin, the initial dosage, platelet count, creatinine level and prior therapy with alkylating agents were found to be significant independent risk factors. For carboplatin, the initial dose, initial platelet count and creatinine levels were the most important factors, but only the dose was statistically significant. Performance status, age, sex or tumour type did not have any independent prognostic value, neither did prior therapy where no alkylating agents were included. This analysis confirms the dose effects. High creatinine levels increases the risk of thrombocytopenia, although they were within the normal range (median: 80 μmol/l; range: 27–148).

We could estimate, from the logistic models, that a dose of 250 mg/m^2 of iproplatin induced the same risk of severe thrombocytopenia (27%) as would a dose of 400 mg/m^2 of carboplatin, for a patient with an initial platelet count of 270 × 10^9/l and an initial creatinine level of 80 μmol/l (median values in our sample).

For patients treated with iproplatin, the percentage reduction in platelet count [PRed(Pla)] was analysed by a multivariate linear regression model. Significant factors included in the final model were the initial dosage ($P = 0.002$), creatinine level ($P = 0.004$), and prior treatment with alkylating agents ($P < 0.001$).

This model was:

(a) for patients not pretreated with alkylating agents:

$$\text{PRed(Pla)} = -33 + 0.27 \times \text{dose} + 0.26 \times \text{creat.}$$

(b) for patients pretreated with alkylating agents:

$$\text{PRed(Pla)} = -16 + 0.27 \times \text{dose} + 0.26 \times \text{creat.}$$

3. *Dose cumulative effect*

The risk of severe thrombocytopenia after prolonged drug administration was estimated by actuarial methods as a function of the total dose previously received by the patient.

Figure 1 shows the cumulative risk (Kaplan–Meier estimate) for both drugs. For patients receiving a total dose equivalent to four cycles of treatment (1200 mg/m^2 of iproplatin or 1600 mg/m^2 of carboplatin), the risk of reaching, at least once, a platelet count below 50 × 10^3/l was estimated at 60%.

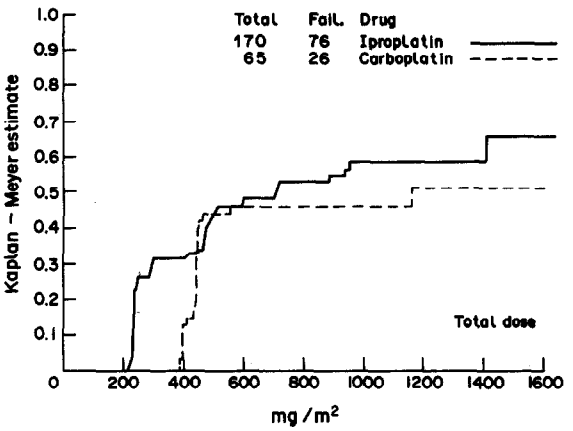

Fig. 1. Risk of severe thrombocytopenia. Kaplan–Meyer estimate.

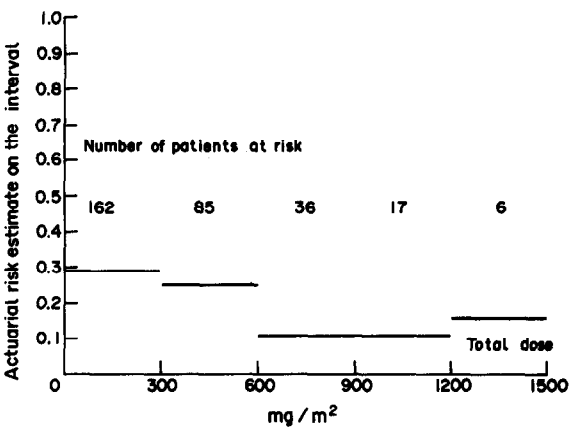

Fig. 2. Risk of severe thrombocytopenia. Actuarial risk estimate on the interval.

Figure 2 shows the hazard rate, estimated by the Gehan method. It is clearly decreasing with the total dose received, but does not reach 0 in our studies. This means that the risk of experiencing severe toxicity for the first time after several cycles of therapy is lower than for the first cycle, but is always present.

Pairwise comparison of nadir platelet and leucocyte counts across cycles, in patients treated without delays, and with a constant dose of iproplatin (240 mg/m^2) demonstrate a significant decrease of those nadirs from the 1st to the 2nd course ($P = 0.014$ and $P < 0.001$ respectively for platelets and leucocytes), from the 2nd to the 3rd course ($P = 0.03$ and $P = 0.5$: n.s.), and from the 3rd to the 4th course ($P = 0.04$ and $P = 0.03$). Too few cases were recorded to be able to analyse further courses, other doses of iproplatin or carboplatin.

With iproplatin, nadir leucocyte count was observed around day 21 at the first cycle of therapy,

Table 4. Non-haematological toxicities across cycles

	Iproplatin	Carboplatin
No. of patients	170	65
Nausea/vomiting	158 (50)*	53 (7)
Diarrhoea	70 (4)	5 (0)
Alopecia	14 (1)	7 (0)
Neurological	13 (1)	1 (0)
Stomatitis	6 (1)	3 (0)
Fever	3 (0)	0 (0)
Allergy	1 (1)	0 (0)
Serum creatinine	10 (0)	7 (0)

*(): WHO grade 3 or 4.

and around day 15 for subsequent cycles, while nadir platelet count was observed around day 15 for all cycles. With carboplatin, both nadir were observed around day 21, in all cycles. Median times to recovery were estimated by the Kaplain–Meier method: thrombocytopenia was recovered significantly earlier (day 28) than leucopenia (day 33); worse levels of thrombocytopenia and of leucopenia were recovered significantly later. However, median time to recovery did not vary significantly with doses, drugs, or across successive cycles (Table 3). These results did not change when only courses of 240 mg/m^2 of iproplatin, that had not been delayed, were taken into consideration. Sample sizes were too small to analyse other dosages or carboplatin courses.

4. *Non-haematological side-effects*

Non-haematological side-effects are summarized in Table 4. Nausea and/or vomiting occurred in 90% of the cases, at a significantly worse level after iproplatin than after carboplatin (P=0.0002). Mild or moderate diarrhoea occurred in 41% of the patients treated with iproplatin, but only in 8% of those patients treated with carboplatin ($P = 0.0002$). Diarrhoea and nausea or vomiting were already significantly more severe after one cycle of treatment with iproplatin than with carboplatin ($P = 0.0002$ and $P < 0.0002$), even in patients not previously treated with cisplatin ($P = 0.009$ and $P = 0.0006$).

Peripheral neuropathy was reported in 6% of the patients on iproplatin (12/170 cases; eight previously treated with cisplatin, one with vincristine, one with both drugs and two with neither of them); marked lethargy occurred in one patient treated with iproplatin and one patient treated with carboplatin. Other side-effects included alopecia (9%), stomatitis (4%) and fever (2%), and one case of severe allergy recorded with iproplatin (oedema of the lips, tongue and larynx associated with shortness of breath and wheezing, relieved with prednisolone). Apart from nausea, vomiting and diarrhoea, no statistically significant differences were observed between the side-effects induced by the two drugs.

Transient increased creatinine levels (above 140 μmol/l) were reported in 11 patients treated with iproplatin, and who are included in the present analysis; in one patient (who had previously received 776 mg/m^2 of cisplatin), it was reported as being initially abnormal. Prior treatment included cisplatin in eight of the 10 remaining patients. One patient not included in the present analysis died of renal failure and liver metastases 45 days after the treatment started. Eight patients receiving carboplatin also had a transient increased creatinine level. In one case, it was clearly related to the disease. All patients but one had received prior chemotherapy, including cisplatin in one case.

5. *Bleeding, infections and toxic deaths*

Bleeding occurred in 18/42 patients with life-threatening (WHO grade 4) thrombocytopenia, and in 3/93 patients with moderate or severe (WHO grade 2/3) thrombocytopenia. Infection occurred in 3/10 patients with life-threatening leucopenia, and in 4/106 patients with moderate or severe leucopenia.

Amongst the 235 patients included in the present analysis, myelosuppression induced seven toxic deaths: four with iproplatin and three with carboplatin. The description of these seven toxic deaths in given in Table 5. All the patients had previously been pretreated with chemotherapy, all but two with cisplatin, and all but two with anthrayclines. They all had normal initial haematological values, and received 240 mg/m^2 of iproplatin or 400 mg/m^2 of carboplatin. The tumour type was stomach in three patients (who died from tumour bleeding), ovary in two patients, testis in one patient and breast in one patient. Lethal haemorrhage related to thrombocytopenia occurred in all cases at the first cycle of treatment. It was associated with severe leucopenia and infection in one case, and with bronchopneumonia and elevated creatinine level in one case.

One additional death could be attributed to iproplatin toxicity (previously described renal failure, associated with liver metastases).

Amongst the 86 patients not evaluable for the present analysis, two toxic deaths were recorded with iproplatin: one patient with testicular cancer died from haemorrhage, but was not included in the general analysis because weekly blood counts were not performed. One patient with head and neck cancer died from renal insufficiency after being treated with gentamycin for a grade 4 infection; this patient was ineligible because prior chemotherapy, including cisplatin, was stopped only 26 days before iproplatin administration.

Table 5. Description of toxic death induced by myelosuppression

Drug Tumour	Iproplatin Ovary	Iproplatin Ovary	Iproplatin Testis	Iproplatin Breast	Carboplatin Stoma.	Carboplatin Stoma.	Carboplatin Stoma.
Age	40	45	28	42	37	48	36
PS	2	1	1	2	2	2	3
Prior chemo.	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Cisplatin	Yes	Yes	Yes	No	No	Yes	Yes
Alkyl. ag.	Yes	Yes	Yes	No	No	No	No
Athracycl.	Yes	Yes	No	No	Yes	Yes	Yes
Antimetab.	No	No	No	No	Yes	Yes	Yes
Init. dose	240	240	240	250	400	400	400
Nr. cycles	1	1	1	1	1	1	1
Total dose	240	240	240	250	400	400	400
Init. WBC cy. 1	5.0	8.8	4.5	5.7	5.7	4.2	8.9
Init. PLA cy. 1	179	234	120	149	141	180	360
Nadir WBC	0.1	4.9	2.9	4.1	0.7	1.4	5.0
Nadir PLA	002	007	009	004	017	010	024
Cause of death	bleed + infect.	bleed	bleed + broncho.	bleed	bleed	bleed	bleed

DISCUSSION

Thrombocytopenia is clearly the most severe side-effect encountered with iproplatin and carboplatin, which confirms the results of all phase I trials [14–18].

Myelosuppression has been proven to be dose-related for iproplatin and carboplatin, within the studied dose ranges. This is suggested by the single variable analysis, and confirmed in the multivariate model. According to this model, doses of 250 mg/m^2 of iproplatin and 400 mg/m^2 of carboplatin appear as equitoxic in terms of thrombocytopenia in the first cycle of therapy, inducing severe thrombocytopenia in 27% of the standard risk patients. This justifies the decision taken by our group, after some experience was acquired with iproplatin, to reduce initial dosages from 300 to 240 mg/m^2. The initial dose of 270 mg/m^2 of iproplatin for good risk patients as recommended by Creaven *et al.* [17] seemed more appropriated than the 300 mg/m^2 recommended by Bramwell *et al.* [18]. In fact, the inferior limit of the dose range for carboplatin (400 mg/m^2) as recommended by Calvert *et al.* should be chosen [14].

Both multivariate models indicate that, for the same dose of iproplatin, only three factors have to be taken into account for predicting thrombocytopenia: (1) the initial platelet count which summarizes all bone-marrow damage induced by any type of prior therapy, except those including alkylating agents; (2) the presence of alkylating agents in prior therapies, which could suggest a synergic effect of those types of drug and iproplatin: this hypothesis should be investigated further; (3) an initially elevated creatinine level, even within the 'normal range': the lack of significance of the factor 'prior cisplatin' after adjustment for creatinine level, and the lack of interaction of those two factors suggest that impaired renal function could be the real cause of increased toxicity (and not a cumulative effect of cisplatin and iproplatin). This finding is consistent with the fact that iproplatin is excreted in the urine, as indicated by the pharmacokinetic studies [8, 9, 19].

Concerning iproplatin, we have proven that these three factors were the most significant. For carboplatin, our data suggest similar results, but the sample size is too small to reach statistical significance. However, this hypothesis is confirmed by Egorin *et al.* [8, 9] who analysed a larger patient sample. In further trials, dose adjustment should be based upon these three factors, instead of considering all types of prior therapy and the performance status.

The percentage reduction in platelet count, as defined by Egorin *et al.* [8], has been investigated by a linear regression model; our data only enabled us to build a similar model for iproplatin. The results are comparable with those generated by Egorin *et al.* for carboplatin, but with small differences: initial creatinine clearance (which plays a major role in Egorin *et al.*'s model) was not measured routinely in our studies but the creatinine level was an important factor in our model. On the other hand, prior chemotherapy was one of the factors of Egorin *et al.*'s model, while prior treatment with alkylating agents appeared in our data as being more relevant.

If we consider patients with an initially normal renal function (creatinine level = 80 μmol/l, creatinine clearance = 60 ml/min.m^2), and having received a prior therapy including alkylating agent, our model becomes:

$$\text{PRed(Pla)} = 4.8 + 0.27 \times \text{dose(iproplatin)}$$

while Egorin *et al.*'s model becomes:

$$\text{PRed(Pla)} = -2.5 + 0.19 \times \text{dose(carboplatin)}.$$

These models are totally comparable: the inde-

pendent factors are negligible, meaning that the models can both be extrapolated to the null dose, and the dose coefficients have about the same ratio (1.42) as the equitoxic doses defined with our logistic models (1.6). According to our model, a dose of 250 mg/m^2 of iproplatin would give a 72.3% platelet reduction and, according to Egorin *et al.*'s model, a dose of 400 mg/m^2 of carboplatin would give a 73.5% platelet reduction, both of these doses having been estimated in patients with an initially normal renal function and pretreated with alkylating agents.

After prolonged treatment with iproplatin, it is difficult to evaluate from our data the extent of thrombocytopenia, because only 27 patients (16%) received more than four cycles of treatment, and often at reduced doses. The actuarial method enables us to estimate at 60% the cumulated risk of severe thrombocytopenia after the administration of 1200 mg/m^2 according to our therapeutic scheme (although this risk was only 30% for the first cycle of treatment). Although there is a risk, after each new drug administration, of inducing severe thrombocytopenia, analysis of the hazard rate indicates that this risk decreases with the total dose. This would infer the hypothesis that the cumulative dose plays more than an additive role, thus being consistent with the observation that the delay of platelets recovery does not increase across cycles, even for patients treated without delays or dose reductions.

In patients treated with 240 mg/m^2 of iproplatin at each cycle, without delay, lower nadir thrombocyte and leucocyte counts are recorded for successive courses. This could be a definition of a dose cumulative effect, as this observation translates anyway the poor feasibility of our dose schedule for a prolonged therapy.

Further studies would be needed to investigate higher total dosages.

Nausea and/or vomiting were recorded in 90% of the patients having received iproplatin or carboplatin, but to a less severe extent with carboplatin, which may be a significant advantage compared to cisplatin. Diarrhoea was also less frequent with carboplatin. These gastro-intestinal toxicities were reported in all phase I trials. The higher frequency of neurotoxicity observed with iproplatin was not statistically significant and was, maybe, related to prior treatment with cisplatin or vincristine.

In our experience, renal toxicity was not a major problem. Some patients had a transient increase in their creatinine level, but only to a severe extent in one case. However, doses were mainly reduced because of thrombocytopenia (which was dose-limiting), and subsequently the evaluation of long-term nephrotoxicity could have been biased.

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