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Dose intensity of carboplatin in combination with cyclophosphamide or ifosfamide*

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Summary. In two separate studies of patients with ovarian cancer, subjects were treated on a protocol comprising 400 mg/m^2 carboplatin in combination with 1 g/m^2 cyclophosphamide (group A) or 5 g/m^2 ifosfamide with mesna (group B). The dose intensities achieved in group A were 87.2 mg/m^2 carboplatin per week and 245.8 mg/m^2 cyclophosphamide per week (34 patients). In group B, the dose intensities achieved were 124.1 mg/m^2 carboplatin per week and 2,020 mg/m^2 ifosfamide per week (25 patients). Two formulae for the prediction of the optimal dose of carboplatin based on renal function and degree of myelosuppression are compared with that based on surface area, and that recently proposed by Calvert is recommended. The importance of dose intensity and the total dose delivered in phase II and III studies is emphasized.

Introduction

Carboplatin has considerable advantages over cisplatin in terms of reduced nausea and vomiting, ease of administration and lower nephrotoxicity [1, 8]. However, the optimal dose has proved to be difficult to determine, as the carboplatin AUC has been shown to be dependent on glomerular filtration and to be subject to considerable inter-individual variation [6]. However, the dose-limiting toxicity is myelosuppression, particularly a decrease in the platelet count [12]. Two formulae have been proposed for the calculation of the optimally safe dosing of carboplatin, one of which is dependent on the glomerular filtration rate alone [3] and the other, on renal function and the pre-treatment platelet count [6, 7].

This study compares the delivered dose of carboplatin with that either planned on the basis of surface area or calculated on the basis of the above formulae in two protocols for the treatment of ovarian cancer in which carboplatin was given in combination with either cyclophosphamide or ifosfamide. The total dose of each drug was also calculated and all dose-related parameters were compared with acute toxicity, pre-treatment characteristics and outcome.

Individualised estimation of the maximally safe dose of carboplatin is essential before a proper comparison of its efficacy with that of cisplatin can be made in phase III studies. Carboplatin is likely to find a place in combination with other agents, particularly alkylating agents such as cyclophosphamide and ifosfamide, which share the dose-limiting myelosuppression of carboplatin.

Patients and methods

Two clinical studies, designated A and B, were analysed for the purpose of this paper. All patients were required to be <70 years old, to have a WHO performance status of 0, 1 or 2 and to have a pre-treatment creatinine clearance of >60 ml/min at study entry. In study A, maximally debulked (residual disease, <2 cm) patients with epithelial ovarian cancer were given a regimen consisting of 1 g/m^2 i.v. cyclophosphamide on day 1 and 400 mg/m^2 i.v. carboplatin on day 8. Six cycles were given at 28-day intervals, and the analysis of dose intensity was carried out over the first four cycles. These patients received no further chemotherapy until relapse occurred.

In study B, patients with unresectable ovarian cancer or residual disease with a diameter of >2 cm received an initial course of three cycles of 400 mg/m^2 carboplatin over 1 h together with 5 g/m^2 i.v. ifosfamide given as a 24-h infusion in 3 l saline containing 2-mercaptoethane sulphonate (mesna) at a dose of 5 g/m^2; a further 3 g/m^2 mesna was given i.v. over the subsequent 8 h. Where toxicity permitted, the ifosfamide dose was escalated by 20% in subsequent cycles. The analyses described below were carried out over the first three cycles of this protocol, following which patients underwent either further resection (if feasible), abdominopelvic radiotherapy (in the case of a complete response), or further chemotherapy (if a partial response had been achieved).

The total dose delivered over the study period was recorded for each drug, as were the duration of treatment delays in weeks and the percent-

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Table 1. Carboplatin dose given in each cycle to group A patients, together with that calculated based on surface area and on formulae 1 and 2

	Cycles:				
Dose (mg)	1	2	3	4	Total dose
Delivered dose	539.7 (119.9)	510.5 (110.9)	485.9 (111.6)	458.0 (90.6)	2,074.4 (510.6)
Calculated (mg/m^2)	640.2 (57.8)	–	–	–	2,560.8 (231.2)
Formula 1	530.3 (102.6)	530.5 (88.9)	518.0 (98)	507.4 (100.4)	2,004.8 (596.6)
Formula 2	660.0 (92.2)	615.6 (147.8)	595.2 (131.2)	610.0 (134.9)	2,473.4 (644.6)
Discrepancy 1[a]	1.8%	3.9%	6.7%	10.8%	3.4%
Discrepancy 2	22.3%	20.6%	22.5%	33.2%	19.2%

[a] Discrepancy represents the maximal discrepancy between the calculated dose and that actually delivered, expressed in percent
Numbers in parentheses represent standard deviations ($n = 33$)

Table 2. Carboplatin dose given in each cycle to group B patients (carboplatin + ifosfamide), compared with the calculated dose based on surface area and on formulae 1 and 2

	Cycles			
Dose (mg)	1	2	3	Total dose
Delivered dose	497.2 (95.2)	481.8 (93.2)	444.5 (79.4)	1,340.6 (265.5)
Calculated (mg/m^2)	614.4 (44.4)	–	–	1,843.2 (177.6)
Formula 1	531.6 (162.1)	508.8 (97.4)	486.3 (100.4)	1,501.6 (395.9)
Formula 2	609.0 (176.3)	594.0 (118.4)	592.5 (133.1)	1,770.0 (396.9)
Discrepancy 1[a]	6.9%	5.4%	9.4%	12.0%
Discrepancy 2	22.5%	23.3%	30.0%	32.0%

[a] D_{max} represents the maximal discrepancy between the calculated dose and that actually delivered, expressed in percent
Numbers in parentheses represent standard deviations ($n = 25$)

age of the intended dose that was actually given after modifications for acute toxicity. The dose intensity of all three drugs was calculated in milligrams per square meter per week according to the formula of Hrynuik and Bush [10], using the treatment time from cycle 1, day 1 to cycle 3, day 1 (group B) and to cycle 4, day 8 (group A).

In both groups of patients, those who received only one cycle (one in group A, three in group B) were excluded from the analysis of total delivered dose and dose intensity. For carboplatin, a comparison was made between the dose calculated according to surface area (m^2), that calculated from the creatinine clearance as proposed by Calvert et al. [3] using the proposed AUC of 5 (Formula 1), as well as that based on creatinine clearance and initial platelet count (Formula 2) [6, 7]. Survival was calculated from the data of the first protocol treatment.

Results

In group A, the mean number of cycles given to 34 patients was 5.2, and patients received a mean total dose of 2,636.2 mg carboplatin and 7.2 g cyclophosphamide. For the analysis of dose intensity over the first four cycles, one patient was excluded from analysis who had received only one cycle, relapsed and died 1 month later. The mean duration of administration of these four cycles was 13.7 ± 3.3 weeks; the carboplatin dose intensity was 87.2 ± 22.7 mg/m^2 per week, and that of cyclophosphamide was 245.8 ± 61.7 mg/m^2 per week. Two other patients relapsed at 16 months and 29 months (median follow-up, 26 months), with carboplatin dose intensities of 48.7 and 76.8 mg/m^2 per week, respectively. Table 1 shows the dose of carboplatin delivered in each of the first four cycles, which fell progressively from a mean of 539.7 mg in the first cycle to 458.0 mg in the fourth (a fall of 15%); these correspond to mean achievable doses of 324.1 mg/m^2 carboplatin per cycle and 772.5 mg/m^2 cyclophosphamide per cycle. It can be seen that formula 2 consistently gave the highest recommended dose, with the values being approximately 20% greater than the doses actually given.

In group B, 20 patients received ≥ 3 cycles of carboplatin and ifosfamide, 5 received 2 cycles, and 3 received just one cycle; a mean total dose of 1,340.6 mg carboplatin and 23.1 g ifosfamide was delivered over the first 3 cycles. Restricting the analysis to the first three cycles and excluding patients who received only one cycle, the mean delay in drug administration was 0.6 weeks. The average carboplatin dose intensity was 124.1 ± 43.3 mg/m^2 per week, and that of ifosfamide was 2.02 ± 0.67 g/m^2 per week. From cycle one to cycle three, the mean dose given fell by 10.5%, from 497.2 to 444.5 mg (Table 2). The doses calculated from formula 1 exceeded those delivered by around 10%, whereas those calculated using formula 2 were 22%–30% greater than those given. These correspond to mean achievable doses of 310 mg/m^2 carboplatin per cycle and 5,358.1 mg/m^2 ifosfamide per cycle. The median survival of group B patients was 14 months, and there was no association between survival and the dose intensity of either carboplatin or ifosfamide.

Changes in the degree of myelosuppression and renal function were also compared in each of the two groups. In group A there was little change in the creatinine clearance (from 81.1 ± 20.5 ml/min to 78.8 ± 19.3 ml/min, over cycles 1–4 whereas the day-1 platelet count fell from $334.0 \pm 113.0 \times 10^9$/l in cycle 1 to $287.5 \pm 105.1 \times 10^9$/l in cycle 4, and the WBC count fell from $4.95 \pm 1.67 \times 10^9$/l on day 1 of cycle 1 to $3.8 \pm 1.79 \times 10^9$/l on day 1 of cycle 4. In group B the creatinine clearance was also little changed, from 84.9 ± 25.8 ml/min in cycle 1 to 74.6 ± 19.7 ml/min in cycle 3. The corresponding figures for platelet counts were 429.0 ± 196.5:$359.5 \pm 164.5 \times 10^9$/l, and those for total WBC counts were 8.09 ± 3.6:$5.5 \pm 2.4 \times 10^9$/l.

Discussion

This paper describes the doses of two-drug combinations used in the treatment of ovarian cancer. The two studies are not strictly comparable, as the group A protocol involved patients with maximally debulked ovarian cancer associated with a relatively good prognosis, given outpatient treatment for a planned duration of 6 months, whereas the

group B protocol was applied to patients with far more advanced disease, inferior performance status, and a correspondingly poorer prognosis. The initial three cycles were given to the latter patients in an attempt to render the disease resectable and to assess both the responsiveness of their tumours to intensive treatment and the side effects associated with this approach.

It can be seen from Tables 1 and 2 that the initial doses given were slightly lower than those calculated precisely on the basis of body surface area, but doses are frequently modified downwards by clinicians to take account of performance status, uncertainty over renal function estimates and vial size. Nevertheless, the data show that it is possible to give carboplatin in combination with cyclophosphamide or ifosfamide consistently, with a dose reduction of only 10%–15% between cycles 1 and 4.

The various formulae cannot be compared in a cumulative manner between cycles, as it is not possible to predict precisely how administration of the highest doses recommended for an earlier cycle would have affected the dose calculations for subsequent cycles. In particular, were the higher doses recommended by formula 2 actually given, they would almost certainly have led to dose modification in subsequent cycles due to myelosuppression as this formula also takes account of platelet count while that of Calvert is based purely on renal function.

The use of body surface area (BSA) as a basis for drug dose calculation was originally proposed by Grollman in 1929 [9] and has come to be widely used in cancer chemotherapy in adults, where this measure is thought to be empirically more appropriate for drugs with a low therapeutic ratio. BSA was found to predict for the highest tolerable dose between animals and man and was subsequently found to correlate with the AUC for some cytotoxic agents [13]. However, for drugs acutely dependent on renal excretion, including carboplatin, it has been suggested that the glomerular filtration rate (GFR) can be more beneficially used to determine the desired AUC, which in turn predicts for the acute dose-limiting toxicity of myelosuppression [6].

Calvert et al. [3, 4] have proposed the formula, dose = AUC (GFR + 25 mg), with a value of between 4.5 and 6 for the AUC, depending on whether carboplatin is used as a single agent or in combination with other drugs and on the desired intensity of treatment, whereas the authors of formula 2 combined prior renal function and bone marrow suppression to arrive at a starting dose. The data in this paper would be consistent with the optimal method being that proposed by Calvert et al. [4], using an AUC value of 5. This formula would appear to most closely predict the doses of carboplatin actually given in combination in consecutive cycles.

The aim of the above prescription method is to establish a dose that can be given repetitively with minimal cause for reduction or treatment delay. The drugs are then given in a schedule which defines the dose rate or dose intensity, and several studies are now trying to maximise this parameter based on the retrospective data of Hryniuk and Bush [10] and Levin and Hryniuk [11], which has yet to be validated in randomised studies. However, these studies may appear to oversimplify the problem of dose: there may be a threshold level below which minimal tumour-cell kill is achieved, and the total dose given or the duration of therapy at a constant dose intensity may also be related to therapeutic effect. All phase II and III studies should now state both the dose intensity and the total dose given to the study population and compare them with the standard endpoints of toxicity, time to relapse and survival.

The present data also demonstrate a higher dose intensity for carboplatin when used in combination with ifosfamide than when used with cyclophosphamide. This difference is only partially explained by the fact that it was calculated over three cycles in group B and over four cycles in group A.

Some relative reduction in the carboplatin dose would also have been expected in group A on account of the day 1 and 8 scheduling chosen for ease of administration as an outpatient. However, the lower myelosuppression associated with the analogue ifosfamide in group B is also likely to be a factor, as has been reported in single-agent comparisons with cyclophosphamide [2]. The pre- and post-treatment values for WBC were both higher in group B than in group A. The high dose intensity of ifosfamide (2,020 mg/m^2 per week) would not have been achieved without the uroprotective agent mesna. The high dose intensities achieved for the combination of ifosfamide and carboplatin makes these drugs suitable for neoadjuvant approaches in tumours with a high proliferation rate, which, in addition to ovarian lesions, may include cancers of the cervix, bladder or oropharynx.

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