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Editorial

Formula-based Dosing for Carboplatin

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IN THIS issue, the paper by Sculier and associates [1] (pp. 1314–1319), discusses a retrospective analysis of data from a large randomised trial where carboplatin dosage was calculated using body surface area. This analysis has shown that thrombocytopenia, the major dose-limiting toxicity of carboplatin, could be related to an estimation of carboplatin exposure calculated by rearranging two published formulae. These formulae are used to individualise carboplatin dose, based on a patient's renal function [2, 3]. The apparent relationship between administered carboplatin exposure or AUC (area under the plasma concentration versus time curve) and thrombocytopenia was present, despite the co-administration of other cytotoxic drugs (cisplatin and ifosfamide). As a result of this analysis, the authors add their support to the use of dosing formulae for carboplatin, based on renal function. The weight of evidence supporting the use of formulae such as that defined by Calvert and associates [2] has convinced many, if not most, clinicians of their utility in reducing unexpected toxicity, the main feature confirmed by Sculier and associates [1].

In 1992 we were fortunate to be given access to a large database containing data from 1028 patients with ovarian cancer, treated with single agent carboplatin [4]. In a similar retrospective analysis, it was possible to identify a 'target carboplatin exposure' which maximised the likelihood of response whilst maintaining toxicity at a manageable level. The chosen exposure or AUC was 7 mg/ml$\times$ min and this was identical to that identified by Calvert and associates [2] for patients previously untreated with chemotherapy. It appeared from our analysis that increasing carboplatin above this exposure would not enhance response rate, despite increasing toxicity. At that time, we were careful to point out that our analysis was retrospective and that data from prospective studies might support or refute our hypothesis. Since that time, there has been published a prospective exposure controlled trial in which patients were randomised to receive either carboplatin AUC 6 (6 cycles) or AUC 12 (4 cycles). In that trial, toxicity was significantly increased in the higher exposure arm, but it was also shown that outcome in terms of response, time to progression and survival was no better, despite the increased morbidity [5].

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The analysis of Sculier and associates [1] did not demonstrate a relationship between outcome, in terms of tumour response and survival, and carboplatin exposure but this is not surprising as carboplatin was administered at relatively low-dose (AUC generally $\leq$4 mg/ml $\times$ min) and in combination with either cisplatin or ifosfamide, active agents in the treatment of patients with non-small cell lung cancer.

It is apparent that the addition of certain other cytotoxic agents does increase the likelihood of thrombocytopenia associated with the administration of carboplatin, although it was not clear in the analysis of Sculier and associates [1] what impact the addition of ifosfamide had. It has been shown that the addition of cyclophosphamide increases the myelotoxicity of carboplatin [6] and this relates to both thrombocytopenia and leucopenia, although the effect on leucopenia was more marked. In the study of Sculier and associates [1] the incidence of thrombocytopenia is greater than would have been predicted, if carboplatin had been administered alone. Using data from the study in patients with ovarian cancer [4], the expected incidence of $\geq$grade 3 thrombocytopenia for carboplatin AUC 4–5 is $<$5%, AUC 5–6; $\sim$10% and AUC 6–7; $\sim$20%. In this study, GFR was measured either by ^{51}Cr-EDTA clearance or measured creatinine clearance. This is in comparison to the incidence of $\geq$grade 3 thrombocytopenia when carboplatin was administered in combination with cisplatin and/or ifosfamide: Carboplatin AUC 3–4; 10%, AUC $>$4; 20%, using the Calvert–Cockcroft approximation or carboplatin AUC 2.5–3; 9%, AUC $>$3; 20%, using the Chatelut method [1]. These data suggest that cisplatin appears to increase the thrombocytopenia associated with carboplatin in these patients, although differences in performance status (PS) between the two patient populations would also need to be performed as PS has also been shown to impact on the likelihood of thrombocytopenia [4]. Pretreatment platelet counts are also likely to be significant as a predictor of subsequent toxicity and indeed this parameter was a feature of the dosing formula of Egorin and associates [7], which targeted a desired platelet nadir, rather than a target carboplatin exposure [7].

Sculier and associates [1] comment that a prospective randomised trial of renal function based dosing versus standard dosing has not been performed, but it is unlikely that such a trial would be feasible as probably very few clinicians would be prepared to expose patients with impaired renal

function to the risk of carboplatin at a dose of 400 mg/m^2 and would wish to dose reduce empirically in such patients. Perhaps their comment suggests some concern that patients may be treated inadequately using a dosing formula. However, in a comparison of patients receiving body surface area based dosing and a matched population receiving formula based dosing, the latter population of patients actually received larger absolute doses (A.H. Calvert, University of Newcastle upon Tyne, U.K.). This highlights the concern that patients receiving a carboplatin dose based on body surface area may actually be the group being undertreated and in certain circumstances, significantly so. In 1028 patients with ovarian cancer, previously untreated with chemotherapy, glomerular filtration rate was 85 ± 32 ml/min [4] suggesting an administered carboplatin mean AUC of 6.4 mg/ml×min for patients with a body surface area of 1.75, i.e. less than the recommended AUC of 7 mg/ml×min. Clearly, approximately 50% of patients will have a GFR >85 ml/min and are all at risk of undertreatment if body surface area dosing is employed.

If, like the majority of clinicians prescribing carboplatin, one is planning to use a dosing formula, particularly that of Calvert and associates [2], there is still some variation in how these are applied. Calvert's formula (dose = AUC×(GFR + 25)) was based on the assumption that glomerular filtration rate (GFR) was estimated using ^{51}Cr-EDTA. The true relationship between GFR and carboplatin clearance was; carboplatin clearance = (0.93×GFR) + 26, which was simplified to formula as we know it today. However, whilst the use of radioisotopes in the assessment of renal function is accepted widely in the U.K., this is not the case in the US and other parts of the world. Also, there are resource implications associated with the assessment of GFR using the ^{51}Cr-EDTA method. Therefore, alternative and simpler methods of GFR estimation have been used and the results substituted into the Calvert formula, possibly causing systematic errors in the calculation of dose in the individual patients. Many of these issues have been reviewed recently [8].

Commonly, 24 h urinary creatinine clearance is used to assess GFR. However, this may be associated with overprediction of GFR due to tubular secretion of creatinine [9, 10], and it has been shown in a group of patients receiving carboplatin chemotherapy that measured creatinine clearance does not correlate well ^{51}Cr-EDTA clearance, the accepted standard measure [11]. However, measured creatinine clearance has been shown to correlate with carboplatin clearance in another study [12] and, therefore, was used by the same group in their dosing formula.

The outpatient collection of 24 h urine specimens is notoriously inaccurate and clearly overnight admission for such an investigation is inappropriate in most settings. Therefore, formulae have been devised to allow the estimation of 24 h creatinine clearance, based on a single plasma creatinine calculation—clearly the most economical approach to the issue. However, it has been shown that both the Jeliffe [13] and Cockcroft and Gault [14] methods underestimate GFR as assessed using ^{51}Cr-EDTA clearance and as a result, will also underestimate carboplatin clearance and hence lead to potential underdosing. It should also be noted that plasma creatinine, and indeed 24 h creatinine clearance, will not give satisfactory estimates of renal function following the previous administration of cisplatin where it has been shown that serum creatinine changes lag behind the cisplatin induced reduction in GFR, as identified by ^{51}Cr-EDTA [15].

In response to these concerns about the use of a surrogate estimate of GFR, one solution is to use the formula of Chatelut and associates [3] where use of the population pharmacokinetic modelling programme, NONMEM, has allowed the development of a formula which estimates carboplatin clearance using the following parameters: serum creatinine, body weight, gender, age. The formula in full is

$$\text{Carboplatin clearance} = (0.134 \times \text{weight}) + \frac{[(218 \times \text{weight}) \times (1 - 0.00457 \times \text{age}) \times (1 - 0.314 \times \text{sex})]}{\text{serum creatinine}}$$

Weight (kg), age (years), sex (0 for male, 1 for female), serum creatinine (μM)

Clearly this does not appear as simple to apply as the Calvert formula, but when one remembers that Cockcroft and Gault are generally used before substituting GFR into the Calvert formula, the time taken to calculate carboplatin dose is probably similar, particularly if a preprogrammed, handheld calculator is used. However, for those continuing to use pen and paper methods, the Chatelut formula might benefit from some simplification of the coefficients used, as the covariates (weight and age) are rarely measured to three significant figures.

One further hurdle stands in the way of the calculation of carboplatin dosage—the issue of the method of serum creatinine estimation, also reviewed recently in this context [8]. Calvert highlights the issue of the imprecision of the calorimetric assay of creatinine, which may overestimate serum creatinine by approximately 20%. Enzymic methods of estimation are more accurate and were used in the development of the formula of Chatelut and associates [3].

An alternative approach to the assessment of renal function, again using NONMEM, has been the development of a formula to estimate GFR, derived from a population PK analysis based on ^{51}Cr-EDTA clearance. This formula uses similar variables to the others (serum creatinine, sex and age), although body surface area (BSA) replaces weight [16].

It would seem preferable that we should move towards a standard dosing formula which is used in all clinical settings, both routine clinical practice and clinical trials, and is based upon serum creatinine measured using the enzymic method, as is the case with the Chatelut formula, but which appears 'on paper', as user friendly as the Calvert formula. This would remove the potential for variable dose prediction dependent upon how the Calvert formula is interpreted. Perhaps the results of the two NONMEM analyses discussed above should be reviewed in collaboration to produce this 'new', user-friendly formula.

In summary, the paper of Sculier and associates [1] lends further support to the concept of formula based dosing of carboplatin. This approach is now used widely and, in my opinion, should be used for all prescribing of carboplatin. Similar formulae have also been developed for the paediatric population. Attention does need to be paid to the exact method used for estimation of renal function and it should be remembered that the original Calvert formula was based on an assessment of GFR using ^{51}Cr-EDTA. Newer formulae are available and are equally easy to apply, even if, at first glance, they appear more daunting.

One would also hope that the careful application of the principles of pharmacokinetics and pharmacodynamics, as has been the case with carboplatin, to other cancer therapeutics will allow the delivery of individualised dosing in many other disease settings.

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