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Editorial Comment

Carboplatin dosing formulae: gender bias and the use of creatinine-based methodologies

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One of the recurring problems of the systemic treatment of cancer is that most of the available agents are active only at toxic doses while the maximum tolerated dose can vary markedly between individuals. Consequently, a dose that will cause serious toxicity in an acceptably small proportion of patients treated will also result in the under-exposure of an unacceptably large proportion of patients.

A classical example of the use of pharmacokinetics to address this problem was the demonstration by Stoller in 1977 [1] that patients who developed serious toxicity following high dose methotrexate treatment were those who retained the drug 72 h after treatment, and that the toxicity could be averted by monitoring the patients blood methotrexate levels and selecting the patients who required additional folinic acid rescue—a technique that is still in use today.

During the early first phase I trials of carboplatin [2,3], it became clear that there was massive interpatient variability in the response of the platelet count to a given dose, measured in mg/m^2. At a dose of 520 mg/m^2, some patients experienced life-threatening grade IV thrombocytopenia, while others maintained normal platelet counts [2]. This led to interest in the pharmacokinetics of the drug where it rapidly became clear that there was a correlation between thrombocytopenia and systemic exposure, as estimated by the area under the concentration×time curve (AUC) [4]. Carboplatin was also found to have fairly simple pharmacokinetics. The majority (approximately 70%) of an injected dose was excreted in the urine with the remainder slowly being inactivated by binding to tissue proteins [4,5]. This, coupled with the observation that the renal elimination was largely due to glomerular filtration, made carboplatin particularly, if not uniquely, susceptible to physiological modelling to predict individualised doses. The first model produced [6] used measures of renal function and of body size to target a dose to a desired level of the pharmacodynamic endpoint, thrombocytopenia. The second [7] simply calculated a dose designed to achieve a pre-defined AUC on the basis that AUC would be a more meaningful indicator of clinical effect to the physician than a dose measured in mg/m^2. The two approaches have become eponymously known as the 'Egorin' and 'Calvert' formulae respectively. These names are simply the first authors of the multi-author papers and their use was not part of the design of the individuals themselves. The Calvert formula has been more widely adopted largely because it can be applied to combination therapy and to high-dose therapy, situations where the use of thrombocytopenia as an endpoint would be inappropriate.

Formula-based dosing was not immediately adopted by the community at large. The first publications on the topic were in 1984 [4] and 1985 [6] (Egorin) and in 1985 [8] and 1989 [7] (Calvert), but the widespread use of the formulae did not start until the early to mid-1990s. Their adoption was largely due to an appreciation that troublesome sporadic severe thrombocytopenia could be averted, making outpatient treatment with low levels of supervision feasible, and the appreciation that it could be done simply using a creatinine-based estimate of renal function. This change in practice owes much to the educational efforts of Bristol-Myers Squibb which did much to increase the awareness of pharmacokinetically-based dosing within the oncology community.

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Without it the adoption of carboplatin as an alternative to cisplatin would have been much more limited.

While it had been possible to demonstrate a correlation between carboplatin AUC and leucopenia or thrombocytopenia in the small pharmacokinetic studies, evidence for such a correlation in a broader population or evidence for any correlation of AUC with therapeutic effect was lacking. Jodrell and his colleagues [9] performed an important retrospective analysis of 1028 patients who had been included in phase II studies for ovarian cancer. These patients had been treated on a mg/m^2 basis, but had had their creatinine clearances measured, so it was possible to form a retrospective estimate of the AUC to which they had been exposed. This study showed a clear progressive increase in haematological toxicity with increasing AUC while the response rate appeared to plateau, with little additional benefit above an AUC of 5 mg/ml×min and almost none above 7. Two prospective studies comparing different AUCs of single-agent carboplatin for the first-line treatment of ovarian cancer have failed to show a significant advantage for the higher AUC. These were comparison of AUC 4 and AUC 8 [10] and a comparison of AUC 6 with AUC 12 [11], although in the latter study dose delays in the high-dose arm meant that the dose intensity was only approximately 20% higher than that in the low dose arm. Two studies performed in (more chemosensitive) germ cell tumours showed contradictory results. Childs and colleagues [12] showed that the relapses occurred almost exclusively in patients exposed to an AUC of less than 4.5, while Bajorin and colleagues [13] were unable to demonstrate this. It should be noted methodological differences may have affected the precision of the AUC calculation. The former authors used the precise ^{51}Cr ethylene diamine tetraacetic acid (EDTA) method for estimating renal function, while the latter used creatinine clearances (see below).

The non-haematological toxicities of carboplatin are minimal compared with those of cisplatin. Nevertheless, studies of high-dose carboplatin suggest that there is a correlation between non-haematological toxicities and AUC. Van Warmedan and colleagues (1996) [14] showed clear correlation of ototoxicity with AUC and Uziely and colleagues (1994) [15] noted that treatment-related deaths on high-dose schedules tended to occur when the AUC exceeded approximately 25.

Thomas and colleagues performed a randomised trial in children with cancer and showed a significant reduction in the variability of the systemic exposure for those patients dosed according to AUC [16]. These authors used a formula derived specifically for use in children, in which the non-renal clearance is varied with body size [17]. There are no randomised trials comparing the therapeutic value of AUC versus mg/m^2 dosing. Bearing in mind the shallow relationship between AUC and response rates observed it is unlikely that such a trial would show a significant difference. Nevertheless, retrospective studies have shown that, if mg/m^2 dosing was used, many patients would receive AUCs below the range documented by Jodrell for optimal effect.

Carboplatin AUC can also be correlated with haematological toxicity in combination therapy. Reyno and colleagues [18] studied 224 women with epithelial ovarian cancer who were treated with a combination of cyclophosphamide and carboplatin. They were able to confirm a relationship between retrospectively calculated AUC and haematological toxicity, and also showed that the addition to cyclophosphamide led to a greater degree of thrombocytopenia for a given AUC than would be expected for single-agent carboplatin. Sculier and colleagues [19] performed a retrospective study using data from a large randomised trial in non-small cell lung cancer. Patients were given cisplatin and carboplatin in combination with or without additional ifosfamide. A significant correlation was found between haematological toxicity and retrospectively calculated AUC, leading the authors to conclude that the therapeutic index of the drug could be improved if AUC-based dosing were used.

The benefits of AUC-based dosing therefore lie in reducing the unpredictability of toxicities and avoiding under-dosing, rather than in increasing the overall therapeutic effect. More recent studies of carboplatin pharmacokinetics have focused largely in three areas. These are (i) deriving a more convenient method for estimating renal function than the ^{51}CrEDTA clearance; (ii) developing more precise methods for achieving a target AUC and (iii) testing the validity of formula-based dosing in combination therapy where there may be pharmacokinetic or pharmacodynamic interactions.

Carboplatin may be assayed by specifically developed high performance liquid chromatographic (HPLC) methods, or by measuring the platinum in the sample by atomic absorption spectrometry. Following administration, carboplatin binds slowly and covalently to plasma proteins to form a biologically inactive adduct, so that there is a progressive decrease in the percentage of plasma platinum that is accounted for by free (or ultrafilterable) platinum and an increase in the percentage accounted for by protein-bound material. The most commonly used measurement for pharmacokinetic studies has been the ultrafilterable platinum level because this can be conveniently measured, reflects the intact carboplatin level and is correlated with thrombocytopenia [4,7,16]. Although platinum can be assayed with precision, there are other potential artifacts that can be introduced into the measurement of plasma and other samples collected as part of carboplatin pharmacokinetic studies. Because the reaction of carboplatin with plasma proteins continues *ex-vivo*, it is necessary to handle samples carefully and properly. This ability of carboplatin to react covalently *ex vivo* means that it is

necessary to chill samples quickly after they have been obtained and either perform the ultrafiltration within minutes or rapidly freeze and store samples at −70 °C. This is because when whole plasma is stored at −20 °C, the free platinum concentration declines with a half-life approximately 30 days [20], whereas at −70 °C it appears to be stable. Other techniques such as the rapid precipitation of the plasma proteins with ethanol have been developed for the measurement of free cisplatin and could be applicable to carboplatin [21]. In at least one study of dose escalated carboplatin, the observed AUCs were 10–15% lower than those predicted and this difference was attributed to the loss of free platinum during sample storage [22]. It is possible that artefacts of sample preparation and storage have also been a factor in reports of 'lower than expected' measured AUCs in other studies where the sample collection and storage conditions are not described.

Mazumdar and colleagues [23] drew attention to a possible source of error in predicting carboplatin AUCs using the 'Calvert' formula. They point out correctly that the formula was derived by performing a linear regression analysis of total plasma clearance (Dose/AUC) on the glomerular filtration rate (GFR), and that the use of the transformed variable (Dose/AUC) could lead to bias due to the estimation of errors, particularly for higher AUCs. They present data on 21 courses of high-dose carboplatin, with target AUCs of 12, 15, 18, 21, 24, 28 or 32. The measured AUC values are very variable and are significantly less than the target for the AUCs of 28 and 32, although not for the lower values. Very little detail of the methodologies and storage conditions are given.

The original derivation of the "Calvert" AUC-based dosing formula used the ^{51}CrEDTA method [24] to estimate the GFR. In this study, the slope of the line correlating ^{51}CrEDTA clearance with total plasma clearance was 0.93 ± 0.08 standard error (S.E.). The data on which the 'Egorin' formula was based showed an almost identical slope of 0.92 despite the fact that the methodologies used were somewhat different [4]. Since the confidence intervals included 1, the carboplatin clearance was assumed to be the same as the ^{51}CrEDTA clearance for the final formula. A careful study by Sørensen and colleagues [25] in which the ^{51}CrEDTA and carboplatin clearances were measured simultaneously showed that the carboplatin clearance was slightly lower than the ^{51}CrEDTA clearance with a mean ratio of 0.77 (range 0.45 to 1.32). This represents a potential source of error in AUC predicted by the formula, although greater errors seem to have been documented as a result of using alternative methods for assessing renal function. While ^{51}CrEDTA clearance provides an accurate estimate of GFR it requires the use of a radioisotope which is not available in all centres. Furthermore, there are many countries where the clinical use of ^{51}CrEDTA is not permitted. Creatinine clearance determined from a 24-h urine collection, or an estimate of creatinine clearance made from the serum creatinine level by the Cockcroft and Gault [26] or Jelliffe [27] formulae have been widely used as substitutes. Huizing and colleagues (1997) [28] performed a study of carboplatin in combination with paclitaxel in which carboplatin doses were calculated on a mg/m^2 basis. Predicted AUCs were measured retrospectively and compared with those directly measured from the pharmacokinetic analysis. The mean predicted AUC was 30% higher than that measured. This observation is probably largely explained by the inaccuracy of the Cockcroft and Gault equation. We have reported that this equation is biased and can under-predict the ^{51}CrEDTA clearance by as much as 50%, with a mean under-prediction of 22% [29]. A similar under-prediction was found with the Jelliffe formula. This under-prediction is probably due to the methodology used for the derivation of the Cockcroft and Gault equation in 1976. Creatinine clearance was calculated in the normal way from the serum creatinine and the 24-h urinary creatinine excretion (urinary volume×urinary concentration/serum creatinine) and the formula was derived using a reciprocal relationship with the serum creatinine level. Thus the same variable, serum creatinine was used in both the dependent and the independent variables of the regression. An alternative explanation for the findings of Huizing and colleagues would be that the co-administration of paclitaxel led to an increase in the clearance of carboplatin. However, this possibility is excluded by other pharmacokinetic studies of the combination [22,30].

Overall, there are few reports of pharmacokinetic interactions between carboplatin and other drugs. The co-administration of the bradykinin analogue, Cereport, produced a small, but not clinically relevant, increase in the AUC of carboplatin [31]. The use of amifostine in combination with carboplatin also produced a higher AUC than when carboplatin was given alone in patients with impaired renal function, possibly as a result of a transient reduction in GFR caused by the amifostine [32]. However, if adducts were formed between amifostine and carboplatin, they would have been measured in the ultrafilterable fraction, although they would not have been biologically active.

The use of creatinine-based methodology for the prediction of carboplatin doses was significantly advanced by Chatelut and colleagues in 1995 [33]. In a seminal paper, they derived a formula to calculate the dose required directly from the serum creatinine level, weight, age and sex. These authors used contemporary population pharmacokinetic analysis techniques (NONMEM) and were able to predict carboplatin AUC with a high degree of precision. This method was subsequently compared with the use of the Jelliffe or Cockcroft and Gault formulae used to estimate the GFR for

the 'Calvert' formula in a number of studies. Van Warmedam [34] found that the Chatelut formula performed with better precision than either of the others, while Okamoto and colleagues [35] obtained the opposite result. These, and other, disparate results in the literature may be explained by the different methodologies used to assay creatinine. These have been reviewed in detail in Ref. [36], but essentially two methods are in common use. One is a colorimetric reaction based on alkaline picrate. This method over-estimates the serum creatinine level by a variable amount, estimated at 10–40%, due to interfering substances, but these substances are not present in urine. The overestimation is reduced by some laboratories by a sample workup designed to remove the contaminants. The renal clearance of creatinine, although mainly accomplished by glomerular filtration, is in part due to tubular secretion. When a 24-h urinary creatinine clearance is measured these two sources of error tend to compensate, leading to an unexpectedly good estimate of the GFR. In addition to creatinine assay methods based on alkaline picrate, there are enzymatic methods in use. These tend not to over-estimate the plasma creatinine level and therefore generate lower values for plasma creatinine and higher values for creatinine clearance. Ando and colleagues have proposed [37] adding a value of 0.2 mg/l to the serum creatinine level when measured using an enzymatic method and have tested this prospectively [38]. In this issue Léger and colleagues describe formula that can be used to convert a plasma creatinine level measured using the colorimetric method to a value that would be expected from an enzymatic assay. They show that this can be used to produce an accurate prediction of AUC conjunction with the Chatelut formula, which was derived using an enzymatic method. Perhaps a more basic approach to the problems of multiple creatinine methodologies is to rework creatinine-based formulae for estimating GFR using an independent isotope method as the independent variable and deriving formulae for different creatinine assay methodologies. Wright and colleagues [39] have recently done this using ^{51}CrEDTA clearance as the standard. Interestingly, this report also showed that the inclusion of the plasma creatine kinase level as a covariate could reduce the bias in the GFR estimate.

The use of any kind of predictive formula for achieving target AUC is still subject to errors, albeit less than those incurred by dosing in mg/m^2. There are also situations, such as in patients with renal failure, in which a formula would not be expected to be reliable. A number of authors have derived minimal sampling strategies, in which a few plasma samples are taken at defined times and used to extrapolate the overall AUC. Since Sørensen and colleagues published the first scheme in 1993 [40], eight additional strategies have been published covering various different schedules of administration of carboplatin [41–48]. These methods are capable of accurate prediction of carboplatin, but because of the necessity for the rapid measurement of plasma carboplatin levels are unlikely to find broad applicability except in special circumstances such as intensive high-dose regimens, paediatric practice [42,46] or in patients with renal failure. Attention has also been given to methods in which the total, rather than the ultrafilterable, plasma platinum has been measured [49,50], since this is a measurement less subject to storage artefact. In particular, Ghazal-Aswad and colleagues [50] showed that it is possible to predict the AUC from the total platinum in a single sample taken 24 h after treatment. Although an independent evaluation [51] showed a slight bias (6%) and greater errors (percentage root mean square prediction error, RMSE% $=20.6\%$) when carboplatin was given in a high dose combination regimen, it nevertheless provides a convenient method with the advantage that it can be used retrospectively, for example following suspected accidental dosage errors.

This issue presents a paper by Dooley and colleagues in which a careful evaluation of the 'Calvert' formula using three different methods for renal function estimation and the Chatelut formula is made. GFR has been estimated using technetium diethylene triaminepentaacetic acid (Tc^{99m}DTPA), a method that the authors have previously demonstrated to give identical results to the ^{51}CrEDTA method. Serum creatinine was measured using an alkaline picrate method, although the authors state the methodology used in their laboratory results in a less than 1.2% variability compared with an enzymatic method. The major findings of the study are the confirmation that the Cockcroft and Jeliffe formulae underestimated the GFR and a new observation that the Chatelut formula predicted significantly lower doses for females than for males. Useful correction factors are suggested for the Cockcroft and Jelliffe formulae. The observation of the gender difference when using the Chatelut formula is used is interesting and is consistent with the data presented by Huitema [47] where the Chatelut formula produced the lowest predicted AUC of nine different methods in a population consisting 43 women and 3 men. Differences in creatinine assay methodology have not been excluded. The creatinine assay used for the development of the Chatelut formula was an enzymatic method based on EKTACHEM Clinical Chemistry Slides (Etienne Chatelut, data not shown, June 1996) as opposed to the alkaline picrate method used here. Nevertheless, this observation deserves further investigation. At the time the study presented here was conducted, the newly derived formulae for the estimation of GFR from plasma creatinine [39] had not been published. However, a comparison of this formula with a minimal sampling strategy [47] suggests that it is reasonably free from bias.

In conclusion, an immense amount of work and talent has been devoted to achieving a precise systemic exposure

to carboplatin, making it unique among anticancer drugs in the precision with which we can calculate the dose. While there are advantages and disadvantages to the various methods, we should not lose sight of the fact that they are all markedly better than using mg/m^2 as a basis for dosing. Based on the normal ranges of GFR encountered in the population, we can expect fourfold or more variability in systemic exposure and a proportion of patients to be seriously under-exposed if mg/m^2 dosing is used. If any of the creatinine-based methodologies is used, the RMSE% is around 25% reducing to approximately 15% for a minimal sampling strategy. When it is appreciated that even an identical AUC may be expected to produce differing degrees of toxicity in individual patients owing to differences in drug handling at the cellular level; that most treatment regimens are combinations with other anticancer drugs, which generate toxicities of their own; and that phenotypic differences in the molecular pathology of tumours can generate massive differences in response to the same cytotoxic event [52], it becomes clear that the oncology community can be proud of their achievements in this area. However, seeking further precision in carboplatin AUC exposure will bring diminishing returns in terms of improved treatment for cancer.

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