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Sewell, GJ

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Dose-banding of carboplatin: rationale and proposed banding scheme

Sabine Kaestner[1]

Graham Sewell[2]

Background. In dose-banding (DB) prescribed doses of cancer chemotherapy are fitted to dose-ranges or 'bands' and standard doses for each band are provided using a selection of pre-filled infusions or syringes, either singly or in combination. DB is used for several drugs where dose is based on body surface area. No DB-scheme has been reported for carboplatin, which, in clinical practice, is routinely dosed according to renal function.

Study objective. To assess the rationale for DB of carboplatin with regards to factors that influence dosing accuracy, develop a DB scheme, and discuss its potential use and limitations.

Methods. Prospective evaluations of carboplatin area under the plasma concentration - time curve (AUC) following application of the Calvert-formula were identified by a literature search. A relevant carboplatin dose range for construction of a DB-scheme with Calvert-formula based doses was obtained from published glomerular filtration rate distributions for patients receiving carboplatin.

Results. A DB-scheme was developed for individually calculated carboplatin doses of 358–1232 mg, with 35 mg increments between each standard dose and a maximum deviation of 4.7% from prescribed dose. The proposed DB-scheme covers the GFR-ranges 47–221 mL/min and 26–151 mL/min for patients receiving doses based on the target AUCs of 5 and 7 mg/mL/min, respectively.

Conclusion. There is a strong scientific rationale to support DB of carboplatin. The proposed banding scheme could introduce benefits to patients and healthcare staff but, as with other DB schemes, should be validated with prospective clinical and pharmacokinetic studies to confirm safety and efficacy. ***J Oncol Pharm Practice (2007) 13: 109–117.***

Key words: Calvert-formula; carboplatin; dose-banding; renal function

INTRODUCTION

The majority of anti-cancer drugs exhibit highly variable inter- and intra-individual therapeutic and toxic effects. Chemotherapy doses are therefore traditionally individualized based on body surface area (BSA), an approach that has been questioned due to its lack of a clear scientific basis.[1,2] For example, the large variability in pharmacokinetic measures, used as surrogate markers for therapeutic/toxic effects, generally does not seem to decrease following this type of individualization.[2,3] In clinical practice, patient specific dose compounding has various disadvantages, including stress for pharmacy and nursing staff and drug wastage when partly used vials are discarded or doses are deferred.[4–6] From the viewpoint of the patient, treatment is often delayed because of a high workload on the pharmacy cytotoxic drug service.[4,5,7] These disadvantages have all become more obvious with the increase

[1]Department of Pharmacy and Pharmacology, University of Bath, Bath BA2 7AY, UK; [2]Department of Pharmacy, Kingston University, Kingston-on-Thames KT1 2EE, UK and Plymouth Hospitals NHS Trust, Plymouth PL6 8DH, UK

Address correspondence and reprint requests to Graham Sewell, Department of Pharmacy, Kingston University, Kingston-on-Thames KT1 2EE, UK
E-mail: G.J.Sewell@kingston.ac.uk

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in cancer chemotherapy treatment.[8] In an attempt to improve this situation, dose-banding (DB) has been proposed as a first step in rationalizing chemotherapy dosing.[4] Plumridge and Sewell[4] defined DB as follows:

Dose-banding is a system whereby, through agreement between prescribers and pharmacists, doses of intravenous cytotoxic drugs, calculated on an individualised basis, which are within defined ranges or bands, are approximated to pre-determined standard doses. The maximum variation of the adjustment between the standard dose and the doses constituting each band is 5% or less. A range of pre-filled syringes or infusions, manufactured by pharmacy staff or purchased from commercial sources, can then be used to administer the standard dose.

DB is dependent on long-term drug stability to enable batch-preparation of standard infusions.[9] This, in turn, permits end-product quality control testing for drug-assay and sterility or aseptic validation.[4] The importance of assuring asepsis in chemotherapy administered to immuno-compromised patients should not be underestimated, because many cytotoxic infusions support the viability of microorganisms.[10,11] DB therefore offers benefits to patient safety and infusion quality that are not possible with individualized doses, which are always used immediately after preparation.

In view of the potential errors and inaccuracies associated with BSA-dose calculations, it has previously been suggested that DB may be particularly appropriate for BSA-dosed drugs.[4] Drugs such as cyclophosphamide, methotrexate, doxorubicin, epirubicin, vincristine, 5-fluorouracil (5-FU), and folinic acid have been successfully dose-banded in the UK, where DB is widely used to provide chemotherapy for oncology outpatients.[4,5,7,12] In these cases, dose-bands have been constructed based on either dose or BSA. In the first case, the individual BSA-based dose is calculated as in current practice, and the dose to be administered with dose-banded syringes or infusions is selected from the DB scheme.[4] In the second case, the DB scheme contains BSA-bands, for example in the range 1.4–2.0 m^2 with 0.05 m^2 intervals, and pre-calculated standard doses based on the mid-point of the BSA-band.[5] In both cases, the banded dose administered is based on the patient's BSA.

Carboplatin is one of the few cytotoxic drugs for which an alternative to BSA dosing is routinely used in clinical practice. The clearance of carboplatin is related to the glomerular filtration rate (GFR), and relationships have been observed between carboplatin exposure (as the area under the plasma concentration - time curve (AUC)) and both its cytotoxic activity and its dose-limiting toxicity, thrombocytopenia.[13–15] Carboplatin doses are therefore commonly calculated based on patient GFR and a target AUC using the Calvert-formula:[13]

$$\text{Dose (mg)} = \text{AUC (mg} \times \text{min/mL)} \times [\text{GFR (mL/min)} + 25]$$

The intra- and inter-patient pharmacokinetic variability for carboplatin may not be eliminated entirely, but this more robust dosing-strategy results in reduced variability compared with BSA-dosing.[13,16–18] Although preliminary results of a clinical and pharmacokinetic study on DB of 5-FU suggest that DB does not alter exposure of the tissues to 5-FU,[19] it may be a different issue to introduce DB for a non BSA-dosed drug such as carboplatin. For drug doses based on BSA, the most important factors affecting drug pharmacokinetics, for example the metabolic capacity of specific enzymes and/or renal function, are not accounted for.[2] DB is therefore less likely to influence the variability in drug exposure of both healthy and tumour tissue and the introduction of an additional random error is not likely to be of clinical significance in BSA-dosed chemotherapy. Given the scientific rationale for dosing carboplatin according to renal function and the perceived reduction in pharmacokinetic variability offered by this approach, the introduction of DB for this drug is more likely to meet with resistance from healthcare professionals. No DB schemes have been reported for carboplatin to date, but no scientific argument, either for or against carboplatin DB, has been put forward. This article describes the rationale for the development of a DB scheme for carboplatin, presents a proposed banding scheme, and discusses its potential use and limitations.

METHODS

Previously, DB schemes have been constructed for doses which are calculated according to patient BSA, as described in the introduction. In this article, the aim was instead to develop a DB scheme for carboplatin doses, which are calculated on the basis of renal function and a target AUC using the Calvert equation.[13]

Table 1a. Magnitudes of carboplatin ΔAUC ($AUC_{observed}$ – $AUC_{predicted}$), expressed as positive deviations, in prospective evaluations of carboplatin exposure following use of the Calvert-formula; GFR estimated with CL_{cr} calculation

Method used for CL_{cr} calculation	Population	$\sqrt{(\Delta AUC)^2}$ (mg × min/mL)	Reference
24 h urine	Adult	0.84	50
CG	Adult	0.46	51
Jeliffe	Adult	0.74	51
Wright	Adult	0.32	51
CG/24 h urine	Adult	0.70	27
CG	Adult	0.99	52
CG	Adult	0.65	52
CG	Adult	1.1	16
CG	Adult	1.2[a]	53
CG	Adult	1.2[a]	31
CG/24 h urine	Adult	0.21	54
Average: 0.77			

[a]*Based on observed versus predicted clearance. Absolute deviations have been re-calculated in cases where the original article expresses them as predictive error, bias (%) or confidence intervals for the slope $AUC_{observed}$ vs. $AUC_{predicted}$.*
AUC, area under the plasma concentration – time curve; CL_{cr}, creatinine clearance, CG; Cockcroft-Gault formula; GFR, glomerular filtration.

Table 1b. Magnitudes of carboplatin ΔAUC ($AUC_{observed}$ – $AUC_{predicted}$), expressed as positive deviations, in prospective evaluations of carboplatin exposure following use of the Calvert-formula; GFR measured by isotopic method

Isotopic method	Population	$\sqrt{(\Delta AUC)^2}$ (mg × min/mL)	Reference
^{51}CrEDTA	Adult	0.80[a]	18
^{51}CrEDTA	Adult	0.48	55
^{51}CrEDTA	Adult	0.12	53
^{51}CrEDTA	Adult	0.06	46
^{51}CrEDTA	Children	0.42	56
^{51}CrEDTA	Children	0.63	56
Average: 0.42			

[a]*Limited sampling used for the determination of AUC. Absolute deviations have been re-calculated in cases where the original article expresses them as predictive error, bias (%) or confidence intervals for the slope $AUC_{observed}$ vs. $AUC_{predicted}$.*
AUC, area under the plasma concentration – time curve; CrEDTA, ^{51}Cr-ethylenediamine-tetraacetic acid; GFR, glomerular filtration.

To provide an understanding of the accuracy of carboplatin dosing and the potential influence of DB on exposure of tissues to carboplatin, prospective evaluations on carboplatin AUC following application of the Calvert-formula were identified by a literature search using PubMed and the keywords 'pharmacokinetics carboplatin Calvert'. Internet-based and manual searches were also performed. The search identified 12 studies over the period 1991–2005. The deviation from the target AUC ($AUC_{observed}$ – $AUC_{predicted}$) was calculated for each study and the ΔAUC data obtained were subjected to squared/squared root transformation to provide positive deviations for comparative purposes. These data are shown in Tables 1a and 1b where GFR was estimated by creatinine clearance (Cl_{cr}), and measured by isotopic methods, respectively.

The first step in designing a DB scheme for carboplatin required the selection of a relevant carboplatin dose range for construction of a DB table. Expected GFR ranges were estimated by comparing several published GFR distributions for cancer patients receiving carboplatin. The carboplatin doses at high- and low-GFR values were then calculated with the Calvert-formula to define the dose range covered by the DB scheme. The construction of the DB scheme followed the same procedure previously reported for drugs where dose calculations were based on BSA.[4] That is, dose increments between each dose-band were

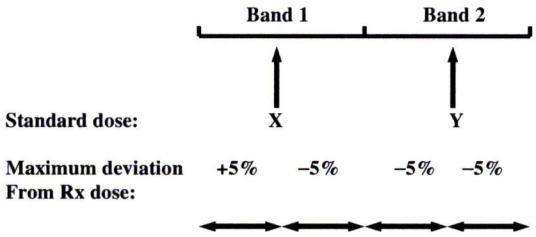

Figure 1. Section of dose-banding scheme showing ±5% maximum deviation of standard doses (*X* and *Y*) from individualized doses within each band.

determined in an iterative process, ensuring that the mid-point dose in each band (the standard dose that would be supplied for that band) did not exceed ±5% of the lowest and highest dose extremities of the constructed band. A maximum deviation of ±5% from the prescribed dose seemed acceptable to most healthcare professionals.[4] For clarification of the banding system see Figure 1.

RESULTS AND DISCUSSION

Variability of carboplatin AUC and justification for DB

The data presented in Tables 1a and 1b show that the measure of exposure of the tissues to carboplatin (AUC) can exhibit variability despite use of the Calvert-formula. This variability may, for example, be caused by either variations in non-renal clearance, most likely in the form of irreversible tissue binding, or by inaccuracies in the methods for GFR-estimation.[13,20] The latter theory is supported by the larger deviation from carboplatin target AUC when creatinine clearance (CL_{cr}) was used to estimate GFR (Table 1a). There was less variability in AUC when the carboplatin dose was calculated from GFR values that were actually measured using isotopic techniques (Table 1b).

Mean GFR-estimates have been observed to vary by 14% across methods in clinical use.[21] Even when using the method initially recommended for GFR measurement in the Calvert-formula, ^{51}Cr-ethylenediamine-tetraacetic acid-clearance (^{51}CrEDTA-CL), there can be considerable deviation from the target carboplatin AUC-values, as shown in Table 1b. This may be due to the use of various methods used for measuring ^{51}CrEDTA-CL. These include the bi-exponential fitting method and the slope-intercept method, in addition to single-sample methods.[20,22] Also, ^{51}Cr EDTA-CL is not accurate in patients with ascites, edema, or other expanded body space, or in patients receiving intravenous hyperhydration therapy.[20] Although the ^{51}CrEDTA method or other isotopic methods, such as ^{125}I-iothalamate-CL or ^{99m}Tc-diethylenetriamine-pentaacetic acid-CL, may be fairly common in some European countries, isotopes are not used for the measurement of renal function in all parts of the world.[23–25] Instead, it is currently common practice to use iothalamate clearance, the CL_{cr} method based on 24-h urine collection, GFR- or CL_{cr} prediction equations, or the Chatelut formula, which predicts carboplatin clearance.[26–32] These equations are based on factors such as age, gender, body weight, race, serum creatinine, urea, and albumin. Cockcroft-Gault is probably one of the most frequently used prediction equations, and the Bjornsson-, Jeliffe-, Wright- and Modification of Diet in Renal Disease Study equations (MDRD1 and MDRD2) are other examples.[26,33–37] All of these equations have been reported to exhibit suboptimal predictive capabilities for ideal patient care. For instance, they may be less accurate in populations that differ from those in which they were developed. Examples include children or elderly, overweight or cachectic individuals, or in cancer patients whose creatinine-, albumin- and urea nitrogen levels may differ from those in healthy people.[24,26,27,33,36,38–43] Using the MDRD2 as an example, 90% of the GFR-predictions have been reported to be within 30% of the isotopically measured GFR.[25] Serum creatinine, a variable used in all equations, is insensitive to small changes in GFR, and is affected by diet, total muscle mass, previous nephrotoxic treatment, as well as other medications that may modify creatinine excretion.[13,24,26,44] Additionally, there are inter-laboratory differences in the calibration, precision, and accuracy of assays used to measure serum creatinine levels, and adjustments have been recommended in some cases.[24,26,28,45]

As carboplatin is dosed to achieve pharmacokinetic endpoints already associated with pharmacodynamic outcomes,[14,46] the errors described above have a clear potential to affect treatment outcomes. The deviations introduced by DB could be additive, or alternatively, they could cancel out some of the already existing errors since random errors tend to eliminate each other.[47] In theory, the maximal deviations from target AUCs introduced by DB can be predicted. As no dose will deviate more than ±5% from the individually (ind) calculated dose, the

Table 2. GFR ranges presented for patients receiving carboplatin in various clinical studies

Study	Number of subjects	Method for GFR-estimation	GFR range (mL/min)
Ghazal-Aswad *et al.*[57]	49	^{51}Cr-EDTA	59–129
Huitema *et al.*[51]	43	CL_{cr}	74–144
Dooley *et al.*[39]	122	Tc^{99m}-DTPA	30–174
Obasaju *et al.*[52]	11	CG	33–88
Calvert *et al.*[13]	18	^{51}Cr-EDTA	33–136
Jodrell *et al.*[14]	1025	various	50–124
van Warmerdam *et al.*[27]	14	CG/CL_{cr}	49–149
van Warmerdam *et al.*[54]	9	CG/CL_{cr}	61–116
Millward *et al.*[18]	40	^{51}Cr-EDTA	39–179
Lin *et al.*[45]	117 (healthy)	Various	70–169
Ando *et al.*[28]	55	Adjusted CL_{cr}	10–146

^{51}CrEDTA, ^{51}Cr-ethylenediamine-tetraacetic acid; CL_{cr}, creatinine clearance; Tc^{99m}-DTPA, ^{99m}Tc-diethylenetriamine-pentaacetic acid; CG, Cockcroft-Gault formula; GFR, glomerular filtration rate.

predicted AUC deviations would remain within the following limits:

$$AUC_{min} = \left[\frac{0.95\,Dose_{ind}}{(GFR+25)}\right] \text{ and}$$

$$AUC_{max} = \left[\frac{1.05\,Dose_{ind}}{(GFR+25)}\right] \Rightarrow$$

$$AUC_{min} = 0.95\,AUC_{ind} \text{ to } AUC_{max} = 1.05\,AUC_{ind}$$

(assuming a constant carboplatin clearance).

Set against the deviations in AUC recorded in published studies (See Tables 1a and 1b) the deviation of ±0.05 mg × min/mL per AUC unit seems insignificant. However, because the observed AUC following exact dosing may often deviate from the predicted AUC in the formula, as shown in Tables 1a and 1b, the absolute change in AUC introduced by DB is not possible to predict. To minimize this uncertainty, it seems reasonable to introduce DB for carboplatin only where GFR has been measured using isotopic clearance methods or alternatives of proven equivalence.

Development of DB scheme for carboplatin

The GFR-ranges reported in the carboplatin trials subjected to review in this study are shown in Table 2, together with the trial sizes and methods for GFR estimation. Based on these GFR-ranges, a DB scheme was developed for individually calculated carboplatin doses of between 358 and 1232 mg, with increments of 35 mg between each standard dose and a maximum dose deviation of 4.7% (Table 3). This DB scheme consequently covers the GFR-ranges 47–221 mL/min and 26–151 mL/min for patients receiving doses based on the target AUCs of 5 and 7 mg/mL/min, respectively. There would be no benefit from including extreme and uncommon doses in the DB scheme since this could increase the number of standard infusions required to provide the dose range, which may not be required before the expiry. In addition, carboplatin is contraindicated in patients with severe pre-existing renal impairment, at a CL_{cr} at or below 20 mL/min (European limit).[48] Unusually low or high doses not covered by the DB scheme would therefore need to be met by individually prepared infusions, as in current practice.

As shown in Table 3, the number of different strengths of pre-prepared standard infusion bags needed to support the proposed DB scheme may vary depending on the number of bags that would be combined to administer one standard dose. Three different schemes are presented in Table 3: For instance, using combination A, nine different pre-prepared infusion strengths would be required if the standard dose was administered using a maximum of two infusion bags in combination. For combinations B and C only seven different pre-prepared infusion strengths would be required if combinations of up to three infusions were used to administer a standard dose. Combinations B and C differ by only one pre-made infusion strength, but are included to illustrate the options available when devising DB schemes. Details of the standard infusions required for this DB scheme are presented in Table 4. In practice, the latter options (combinations B and C, using up to three infusions) are not likely to introduce any difficulty compared with the

Table 3. Dose-banding scheme for pre-filled carboplatin infusions, showing three possible combinations (A, B, and C) of pre-made infusions to provide the standard dose for each band. Each strength of pre-made infusion is shown in bold type at first use

Dose calculated according to ^{51}CrEDTA–CL (mg)	Dose to be supplied using pre-filled infusions (mg)	Deviation from individualized dose (%)	Mean √deviation^2 (%)	Infusion combination A (if two bags) → 9 strengths	Infusion combination B (if three bags) → 7 strengths[a]	Infusion combination C (if three bags) → 7 strengths[a]
358–392	375	−4.3–4.7	4.50	**375**	**375**	**375**
393–427	410	−4.0–4.3	4.15	375 + **35**	375 + **35**	375 + **35**
428–462	445	−3.7–4.0	3.85	375 + **70**	375 + **70**	375 + 35 × 2
463–497	480	−3.4–3.7	3.55	375 + **105**	375 + 70 + 35	375 + **105**
498–532	515	−3.2–3.4	3.30	375 + **140**	375 + 70 × 2	375 + 105 + 35
533–567	550	−3.0–3.2	3.10	**550**	**550**	**550**
568–602	585	−2.8–3.0	2.90	550 + 35	550 + 35	550 + 35
603–637	620	−2.7–2.8	2.75	550 + 70	550 + 70	550 + 35 × 2
638–672	655	−2.5–2.7	2.60	550 + 105	550 + 70 + 35	550 + 105
673–707	690	−2.4–2.5	2.45	550 + 140	550 + 70 × 2	550 + 105 + 35
708–742	725	−2.3–2.4	2.35	**725**	**725**	**725**
743–777	760	−2.2–2.3	2.25	725 + 35	725 + 35	725 + 35
778–812	795	−2.1–2.2	2.15	725 + 70	725 + 70	725 + 35 × 2
813–847	830	−2.0–2.1	2.05	725 + 105	725 + 70 + 35	725 + 105
848–882	865	−1.9–2.0	1.95	725 + 140	725 + 70 × 2	725 + 105 + 35
883–917	900	−1.9–1.9	1.90	**900**	**900**	**900**
918–952	935	−1.8–1.9	1.85	900 + 35	900 + 35	900 + 35
953–987	970	−1.7–1.8	1.75	900 + 70	900 + 70	900 + 35 × 2
988–1022	1005	−1.7–1.7	1.70	900 + 105	900 + 70 + 35	900 + 105
1023–1057	1040	−1.6–1.7	1.65	900 + 140	900 + 70 × 2	900 + 105 + 35
1058–1092	1075	−1.6–1.6	1.60	**1075**	**1075**	**1075**
1093–1127	1110	−1.5–1.6	1.55	1075 + 35	1075 + 35	1075 + 35
1128–1162	1145	−1.5–1.5	1.50	1075 + 70	1075 + 70	1075 + 35 × 2
1163–1197	1180	−1.4–1.5	1.45	1075 + 105	1075 + 70 + 35	1075 + 105
1198–1232	1215	−1.4–1.4	1.40	1075 + 140	1075 + 70 × 2	1075 + 105 + 35
			Average: 2.41%			
			Median: 2.15%			

[a]*Combinations B and C are alternative schemes which differ in that the 70 mg standard infusion in B is replaced by a 105 mg infusion in C.*
^{51}CrEDTA-CL, ^{51}Cr-ethylenediamine-tetraacetic acid clearance.

Table 4. Pre-filled infusions used in DB scheme (Table 3)

Dose in DB scheme (mg)	Final infusion volume in 5% glucose (mL)	Infusion strength (mg/mL)
35	50	0.70
70	50	1.40
105	50	2.10
140	100	1.40
375	500	0.75
550	500	1.10
725	500	1.45
900	500	1.80
1075	500	2.15

DB, dose-banding.

first option (combination A). This is because the approach anticipates the use of a multi-valve manifold, to which up to four infusions/flush liquids may be connected. Examples of this type of administration set are available from Codan and Baxter.

The DB scheme in Table 3 is dependent upon the batch manufacture of standard infusions to provide pre-prepared doses, as, and when required. This in turn is dependent upon extended stability of these infusions. We have demonstrated the physical and chemical stability of the infusions used in this scheme (Table 4) over 84 days under refrigerated storage followed by additional 'in-use' periods at room temperature.[9]

As with all DB initiatives, there is a compelling, if belated, need for clinical studies to justify the safety and efficacy of this approach. An ongoing pharmacokinetic study has therefore been designed to evaluate DB of carboplatin using the scheme in this article with AUC as the key outcome measure. To justify carboplatin DB with drug stability data and pharmacokinetic studies may still not be entirely sufficient. In general, staff in oncology pharmacy units and oncology nurses are in favor of DB.[4,12] However, the opinions and clinical judgments of the prescribing oncologists are also factors which may be crucial to the uptake of DB. For example, some may support the view that considering the intra- and inter-individual differences in drug handling at the tumoural- and cellular levels, the clinical value of increased precision in AUC-targeted dosing of carboplatin is likely to be limited,[49] whereas others believe in exact dosing. In a recent national survey among UK oncologists performed by the authors, 95% (of 369 evaluable respondents) were in favor of DB, while 57% of these held the opinion that DB of carboplatin would be acceptable. Of the remaining oncologists, 21% did not know if carboplatin DB would be acceptable or thought that it may be possible, while 21% did not support carboplatin DB. A full report on this survey will be published elsewhere. The availability of data on safety and efficacy to provide an evidence base for carboplatin DB, together with a wider understanding of the potential benefits of DB, is likely to further increase support for this approach.

CONCLUSION

A rationale has been proposed for DB of carboplatin, and the general clinical opinion seems to support further studies on the subject. As with all DB schemes, the introduction of the system is dependent on clinical and pharmacokinetic data to establish whether DB introduces any clinically significant alterations in the exposure of both healthy and malignant tissues to carboplatin. Subsequently, the application of carboplatin DB to doses calculated using alternative methods to isotopic clearance for GFR estimation, should also be evaluated.

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