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CARBOPLATIN DOSING FOR ADULT JAPANESE PATIENTS

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ABSTRACT

Carboplatin is a platinum-based anticancer drug that has been long used to treat many types of solid cancer. Because the clearance of carboplatin strongly correlates with the glomerular filtration rate (GFR), its dosage is calculated with the Calvert formula on the basis of the patient's GFR to achieve the target area under the plasma drug concentration-time curve (AUC) for each patient. However, many lines of evidence from previous clinical studies should be interpreted with caution because different methods were used to estimate drug clearance and derive the dosage of carboplatin. There is a particularly high risk of carboplatin overdosing when the dosage is determined on the basis of standardized serum creatinine values. When deciding the dose of carboplatin for adult Japanese patients, preferred methods to assess renal function instead of directly measuring GFR include (1) 24-h urinary collection-based creatinine clearance adjusted by adding 0.2 mg/dl to the serum creatinine concentration measured by standardized methods, and (2) equation-based GFR (eGFR) with a back calculation to units of ml/min per subject. Given the limitations of serum creatinine-based GFR estimations, the GFR or creatinine clearance should be directly measured in each patient whenever possible. To ensure patient safety and facilitate a medical-team approach, the single most appropriate method available at each institute or medical team should be consistently used to calculate the dose of carboplatin with the Calvert formula.

Key Words: carboplatin, pharmacokinetics, creatinine clearance

CLINICAL PHARMACOLOGY OF CARBOPLATIN

Carboplatin, a platinum-based anticancer drug, has long been used to treat many types of solid cancer, such as ovarian cancer and non-small-cell and advanced small-cell lung cancers (Fig. 1). Similar to the mechanism of cisplatin action, carboplatin covalently binds to DNA to form DNA-platinum adducts that induce apoptosis of cancer cells. Carboplatin shows some cross-resistance with cisplatin. However, carboplatin is fairly distinct from cisplatin with respect to toxicity and dosing strategy. Unlike cisplatin, carboplatin usually does not cause nephrotoxicity or severe nausea or vomiting; instead, its dose-limiting toxicity is myelosuppression, mainly thrombocytopenia. Therefore, carboplatin is frequently used instead of cisplatin in patients with

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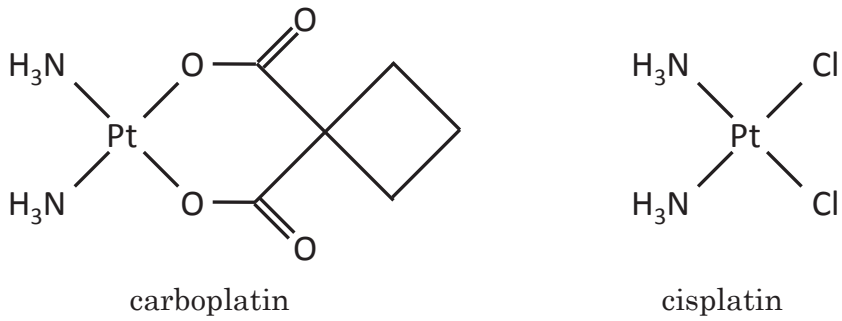

Fig. 1 Chemical structures of carboplatin and cisplatin

platinum-sensitive cancer who are unable to tolerate cisplatin-related toxicity or the aggressive hydration needed to prevent nephrotoxicity. The marked difference in toxicity is explained in part by the distinctive pharmacokinetics of carboplatin: most importantly, carboplatin is more stable in plasma than cisplatin. During the first 4 hours after intravenous administration, more than 90% of carboplatin remains unbound to plasma proteins. Most of the remainder slowly binds to plasma proteins over the course of the next 24 hours.[1] Because carboplatin is predominantly filtered and eliminated by the renal glomerulus, clearance of the drug strongly correlates with the glomerular filtration rates (GFR) of individual patients. The linear pharmacokinetics of carboplatin is another key to understanding its dosing strategy: the drug clearance is constant, at least across the therapeutic range. Consequently, there is a strong linear correlation between the patient's GFR and the area under the plasma drug concentration-time curve (AUC) after administration of carboplatin, which means that GFR simply determines the actual AUC for each patient.

The AUC of carboplatin closely reflects total body exposure to the drug. In fact, carboplatin-related thrombocytopenia and other toxic effects, as well as antitumor efficacy, depend on the AUC rather than on the administered dose based on body surface area (BSA).[2] Therefore, unlike most anticancer drugs for which dosage is determined on the basis of the patient's BSA, the dosage of carboplatin is calculated using the GFR of the individual patient to achieve the target AUC. For adult patients with cancer, the Calvert formula has been commonly used for such pharmacokinetic-guided dosing.[3]

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

The clinical superiority of this GFR-based dosing over conventional BSA-based methods has not been demonstrated. However, multiple pharmacokinetic studies have shown that the GFR-based dosing reliably attains the target AUC with acceptable toxicity and therapeutic efficacy in patients who receive carboplatin.

CARBOPLATIN DOSING WITH THE CALVERT FORMULA

GFR is the best overall index of renal function. Exogenous inert substances, such as inulin, iohexol, or iothalamate, which are filtered freely by the glomerulus and neither reabsorbed nor secreted *via* the renal tubules, are considered the best filtration markers for the measurement of GFR.[4] Inulin clearance is now used clinically in Japan.

$$\text{Inulin clearance (ml/min)} = \frac{\text{urine volume (ml/min)} \times \text{urine inulin (mg/dl)}}{\text{serum inulin (mg/dl)}}$$

The Calvert formula was developed using the GFR measured by assessing the clearance of ^{51}Cr-ethylenediamine tetraacetic acid (^{51}Cr-EDTA), a radionuclide-labeled GFR marker. However, because it is not realistic to measure such uncommon exogenous substances in routine practice, creatinine clearance (CrCl, ml/min) at steady state has been historically used instead of GFR. CrCl is generally used to adjust the dosage of drugs that are mainly excreted by the kidney.

$$\text{CrCl} = \frac{\text{urine volume (ml/min, usually over 24 hours)} \times \text{urine creatinine (mg/dl)}}{\text{serum creatinine (mg/dl)}}$$

To avoid the use of urine collection bags and inaccuracies associated with urine collection, it is a widely accepted practice to use mathematical equations to estimate CrCl (eCrCl) on the basis of a single measurement of serum creatinine.[5,6]

Cockcroft-Gault equation:

$$\text{eCrCl} = \frac{\text{weight (kg)} \times \{140 - \text{age (years)}\}}{72 \times \text{serum creatinine (mg/dl)}} \ (\times\ 0.85 \text{ if female})$$

Jelliffe equation:

$$\text{eCrCl (ml/min/1.73 m}^2) = \frac{98 - 0.8 \times \{\text{age (years)} - 20\}}{\text{serum creatinine (mg/dl)}} \ (\times\ 0.9 \text{ if female})$$

In response to an increasing need to precisely estimate GFR (eGFR) and thereby detect renal dysfunction at an early stage, the Modification of Diet in Renal Disease (MDRD) Study equation and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation were recently developed in the US. As the Japanese counterpart, an alternative equation has been developed.[7]

$$\text{eGFR (ml/min/1.73 m}^2) = 194 \times \text{serum creatinine (mg/ml)}^{-1.094} \times \text{age}^{-0.287} \ (\times\ 0.739 \text{ if female})$$

It is noteworthy that eGFR incorporates a correction factor for standard BSA (ml/min/1.73 m^2). Therefore, when used for the Calvert formula, eGFR must be back-calculated to translate into units of ml/min per subject, using the individual patient's BSA.

$$\text{eGFR (ml/min)} = \text{eGFR (ml/min/1.73 m}^2) \times \frac{\text{BSA (m}^2)}{1.73}$$

PITFALLS IN CARBOPLATIN DOSING BASED ON SERUM CREATININE

Although pharmacokinetic-guided dosing using the Calvert formula has gained general acceptance in medical oncology, pitfalls in estimating GFR for carboplatin dosing have been recently discussed. First, unlike inulin and other GFR markers, creatinine is secreted by the renal tubules in addition to glomerular filtration; therefore, CrCl is expected to exceed GFR

normally by 5% to 15%. When the Jaffè method, a traditional colorimetric assay, was used to measure serum creatinine in the past, the difference between CrCl and GFR was almost negligible in clinical practice. The serum creatinine concentration measured by the Jaffè method was systematically higher than the true concentration by 0.1 to 0.3 mg/dl owing to interference by non-specific substances in the serum. Accordingly, the calculated CrCl was underestimated but remained close to the GFR. However, as creatinine-specific assays, employing techniques such as enzymatic methods, isotope dilution mass spectrometry (IDMS), or IDMS-traceable methods, became standardized in clinical laboratories during the past decade, this inherent difference was sometimes no longer negligible clinically. For the majority patients and for most drugs, there is actually little difference in the dosage based on either CrCl or GFR because dosage modification is simply categorized; for example, the dose should be reduced by one level in the event of impaired renal function. On the other hand, overestimation of carboplatin clearance does have a serious impact on carboplatin dosing because even a small overdose can cause unexpected severe toxicity owing to the narrow therapeutic index. In Japan, enzymatic methods have been commonly used in clinical laboratories since the middle of the 1990s, whereas major laboratories in the US launched IDMS or IDMS-traceable methods by the end of 2010. In the European Union and perhaps other countries, the measurement of serum creatinine has yet to be standardized.[8] The time-lag between Japan and other countries in introducing standardized methods seems to have caused considerable confusion about carboplatin dosing. Carboplatin dosages based on standardized methods are expected to be higher than those used in previous clinical studies, in which the dosage was calculated by non-standardized methods. We first warned about important bias in 1997 (Fig. 2),[9] and subsequently proposed a correction formula for the adjustment of serum creatinine concentration measured by the standardized method.[10-12] This correction formula cannot overcome the bias completely, but we consider that it carefully balances between avoiding the risks of overdosage and improving the therapeutic efficacy in patients given carboplatin.

$$\text{Adjusted CrCl} = \frac{\text{urine volume (ml/min)} \times \text{urine creatinine (mg/dl)}}{\text{serum creatinine (mg/dl)} + 0.2}$$

However, many physicians did not pay much attention to this bias until standardized creatinine methods were recently introduced in the US. In 2010, the US Food and Drug Administration and Gynecologic Oncology Group alerted the investigators participating in clinical trials of carboplatin that the incidence of carboplatin-related toxicity increased after introduction of the standardized method.[13] They recommended (1) to use the Cockcroft-Gault equation instead of the Jelliffe equation; (2) to cap carboplatin dosage using a maximum GFR of 125 ml/min in the Calvert formula, corresponding to 900 mg, 750 mg, and 600 mg at AUC of 6, 5, and 4, respectively; and (3) to round abnormally low serum creatinine concentrations to 0.6 mg/dl (amended to 0.7 mg/dl soon after). Although these modifications were immediately effective for ensuring patient safety, they most likely did not enhance therapeutic efficacy.

A second pitfall is that eGFR and eCrCl derived from serum creatinine concentrations are not ideal markers of renal function. Because creatinine is an endogenous substance, serum creatinine concentrations inevitably depend on various non-renal factors, such as muscle mass, dietary intake, drug interactions, and variability among assays. The effects of these factors are more evident in patients with advanced cancer, who have distinctive physiological and nutritional status and are likely to receive multiple medications. Accordingly, the serum creatinine concentrations in such patients are frequently in a non-steady state. Furthermore, because the Cockcroft-Gault and the Jelliffe equations were developed when serum creatinine concentrations were measured by non-standardized methods, the eCrCl estimated on the basis of the current standardized creatinine-

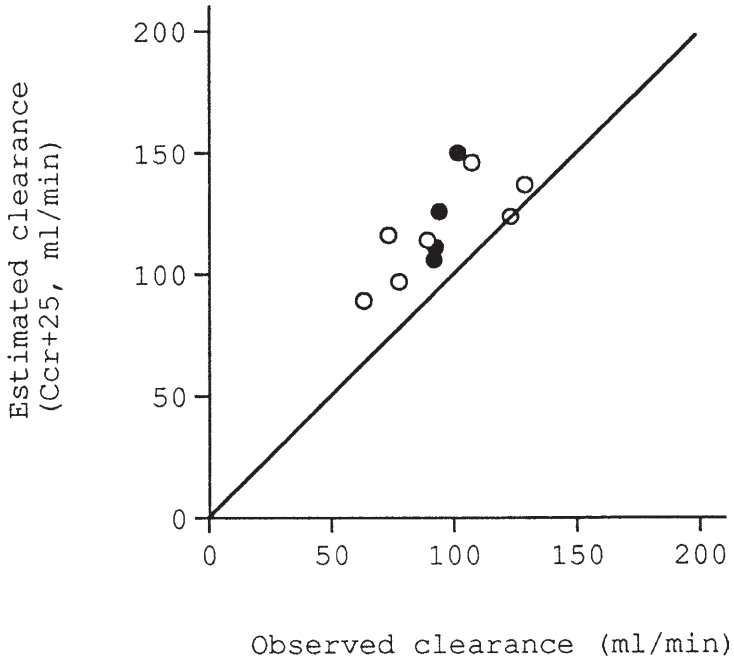

Fig. 2 Scatter plots of carboplatin clearance estimated by Calvert's formula versus observed clearance. The clearance estimated on the basis of crude 24-h creatinine clearance was systematically higher than the actual clearance. The serum creatinine concentration was measured by enzymatic method. Closed circles represent patients who had received prior chemotherapy with cisplatin. The line denotes complete agreement between the estimated and observed clearance. Reproduced from Ando *et al.* with permission.[9)]

specific method is systematically higher and less accurate.[14)] We should bear in mind that eCrCl, used to adjust dosage in the package inserts of most drugs, was calculated with non-standardized methods that are no longer in use. Given these limitations of serum creatinine-based eGFR and eCrCl, the GFR or CrCl should be directly measured in each patient whenever possible. Similarly, the so-called Chatelut formula, another way of estimating carboplatin clearance from serum creatinine concentrations and patient characteristics, overestimates carboplatin clearance when the serum creatinine is measured by standardized methods.[11,15)]

Finally, the Calvert formula requires GFR that is not adjusted for a standard BSA of 1.73 m^2. Therefore, eGFR and eCrCl derived from the Jelliffe equation must be translated into units of ml/min per subject. In a pivotal phase I study of carboplatin with paclitaxel in patients with ovarian cancer, the CrCl was estimated with the Jelliffe formula, but back-calculation to units of ml/min per subject was not required, which seems to have had a considerable impact on subsequent clinical studies of carboplatin for the disease.[16)]

HOW SHOULD WE CALCULATE CARBOPLATIN DOSAGE FOR JAPANESE PATIENTS?

The package insert for carboplatin in Japan states that the starting dose is 300 to 400 mg/m^2 on the basis of BSA for patients with normal renal function. In addition, nonspecific safety information recommends dose reduction for patients with impaired renal function. However,

AUC-based pharmacokinetic-guided dosing using the Calvert formula would be better than giving a flat dosage or BSA-based dosage with respect to patient safety and therapeutic efficacy.

The question arises as to how we should estimate carboplatin clearance and determine the dosage for adult Japanese patients? Clearly, it is not practical to routinely measure inulin-based GFR to assess a patient's renal function. Therefore, 24-h urinary collection-based CrCl adjusted by adding 0.2 mg/dl to the standardized serum creatinine concentration is currently most preferable. Similarly, eGFR with a back calculation to units of ml/min per subject is acceptable when urinary collection is difficult or a patient has to start chemotherapy immediately, albeit a single measurement of serum creatinine has inherent limitations. There is no evidence to support the use of equation-based eCrCl after adding 0.2 mg/dl to the standardized serum creatinine concentration. However, adjustment of the serum creatinine concentration is at least necessary when treatment is based on prior clinical studies that used the eCrCl derived from non-standardized serum creatinine concentrations for carboplatin dosing.

To evaluate which GFR assessment provides better performance with respect to carboplatin dosing, we investigated carboplatin pharmacokinetics in 21 Japanese patients in whom GFR was exactly measured on the basis of inulin clearance.[17] Use of the adjusted 24-h CrCl gave estimated carboplatin clearance closest to the inulin clearance (GFR), whereas crude 24-h CrCl overestimated carboplatin clearance by more than 30% (Table 1). Interestingly, even the use of inulin clearance overestimated the actual clearance (dose/AUC), suggesting that the original Calvert formula inherently might cause overdosing, at least in adult Japanese patients. We suppose that the non-renal clearance of carboplatin in the formula, corresponding to a constant value of 25, might be too high for Japanese patients.

Because the Calvert formula was developed on the basis of data from patients with GFR ranging from 33 to 135 ml/min, we validated its usefulness in 2 Japanese patients who were undergoing hemodialysis (Table 2).[18] The dosages were calculated using the Calvert formula, in which the GFR was assumed to be 0 (no renal function), with a target AUC of 4 (100 mg) or 5 (125 mg). Hemodialysis was started 24 hours after the initiation of carboplatin infusion. The results of pharmacokinetic analysis revealed that the actual AUCs (4.7 and 6.1) were about 20% higher than the target values, but were within the clinically acceptable range. The pre-dialysis body clearance, which closely corresponded to the non-renal clearance, was about 16 ml/min in both patients, again supporting the hypothesis that the constant 25 in the Calvert formula might be too high for adult Japanese patients.

A single dose of carboplatin is the standard of care for adjuvant therapy of stage I testicular seminoma. In a pivotal study demonstrating the non-inferiority of a single dose of carboplatin to radiotherapy, patients received carboplatin at a target AUC of 7 on the basis of radioisotopic measurement of GFR.[19] When 24-h urinary collection-based CrCl was used instead of GFR, the dose was reduced to 90% (<AUC 7) to avoid overdosage caused by the overestimation of carboplatin clearance. The poorer 5-year relapse-free survival of patients given a dose of <AUC 7 underlines the importance of accurately determining GFR in patents who receive this potentially curative treatment. For this reason, the measurement of inulin-based GFR is mandatory in patients with stage I testicular seminoma who are scheduled to receive adjuvant therapy with carboplatin at Nagoya University Hospital.

CONCLUSIONS

Many oncologists have long believed that pharmacokinetic-guided dose setting of carboplatin with the Calvert formula is the most successful example of personalized chemotherapy, particu-

Table 1 Evaluation of various methods to estimate carboplatin clearance*

Estimated carboplatin clearance	MPE ± SE (%)	RMSE (%)
GFR (inulin) + 25	14.3 ± 5.7	29.2
24-h CrCl + 25	35.4 ± 9.2	54.3
Adjusted 24-h CrCl + 25	15.0 ± 8.6	41.3
Estimated CrCl + 25	26.1 ± 9.5	49.8
Estimated GFR + 25	20.3 ± 8.9	44.5

*Actual carboplatin clearance (ml/min) was calculated by dividing the administered dose (mg) by the measured AUC (mg⁄ml × min). GFR was measured as inulin clearance. Estimated CrCl was calculated using the Cockcroft-Gault equation. Adapted from Shimokata *et al.*[17]

Abbreviations: GFR, glomerular filtration rate; CrCl, creatinine clearance; MPE, mean predictive error, SE, standard error; RMSE, root mean squared error; AUC, the area under the plasma drug concentration-time curve.

Table 2 Pharmacokinetic parameters of carboplatin in patients who are undergoing hemodialysis

Parameter	Patient 1	Patient 2
Dose (per subject)	100 mg	125 mg
C_{max} (μg/ml)	6.47	9.27
AUC (mg/ml × min)		
Target	4	5
Pre-HD	3.9	5.52
Post-HD	0.58	0.36
Total	4.7	6.1
Pre-HD $T_{1/2}$ (h)	17.5	13.8
Pre-HD CL (ml/min)	16.1	16.5

C_{max}, maximum plasma concentration; AUC, the area under the plasma drug concentration-time curve; HD, hemodialysis; $T_{1/2}$, elimination half-life, CL, plasma body clearance.

larly as compared with the classic practice of basing the dose on BSA. However, increasing concern has been raised about this strategy because previous clinical trials have used different methods to estimate drug clearance for carboplatin dosing. There is a particularly high risk of carboplatin overdosing when the dosage is based on the standardized serum creatinine concentration. Therefore, many lines of clinical evidence should be interpreted with caution when applied to current patients. Besides measuring inulin-based GFR, currently recommended methods to assess renal function for the Calvert formula include (1) 24-h urinary collection-based CrCl adjusted by adding 0.2 mg/dl to the standardized serum creatinine concentration, and (2) eGFR with a back calculation to units of ml/min per subject. To ensure patient safety and facilitate a medical-team approach, the single most appropriate method available at each institute or medical team should be consistently used to calculate the dose of carboplatin with the Calvert formula.

CONFLICT OF INTEREST

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