

Carboplatin Dosing Update

Maggie Ning, Pharm.D. Intern and Leticia Smith, Oncology Clinical Pharmacy Specialist

Background: ¹⁻⁴

Carboplatin belongs to the class of platinum-containing antineoplastic agents, which also includes cisplatin and oxaliplatin. Carboplatin, a second generation analog of cisplatin, has cytotoxic activity similar to cisplatin. Once inside the cell, carboplatin is hydroxylated by water to form the active compound, then it covalently binds to DNA at two sites, forming interstrand and intrastrand cross-links. This irreversible binding results in the inhibition of DNA replication. Carboplatin is a cell cycle non-specific agent with increased activity during the S-phase. It causes cell cycle arrest in the G₂-phase; then induces cellular apoptosis.

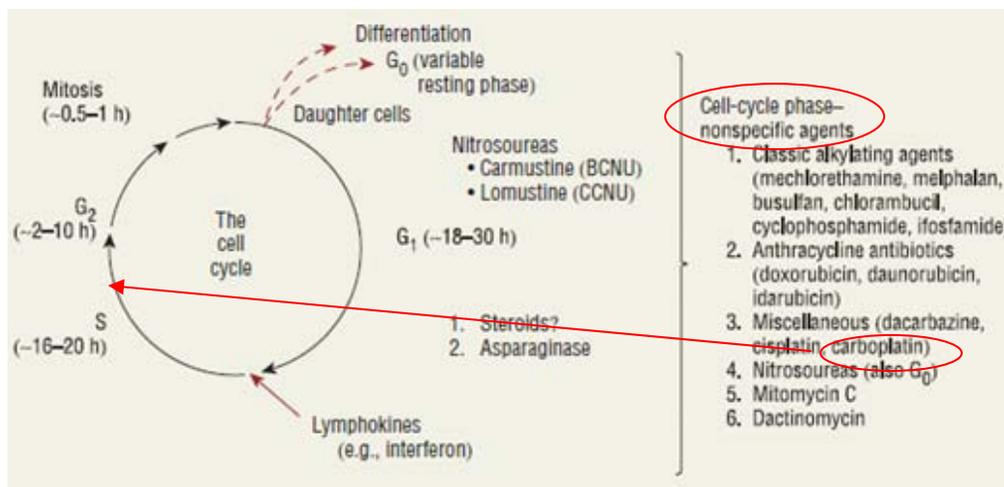


Figure 1 shows various antineoplastic agents and their activities in the cell cycle.

Carboplatin is administered primarily through IV infusion. Unlike cisplatin, it has minimal protein binding and distributes well into ascites, pleural fluid, liver, kidney, skin and tumor tissues. Carboplatin has minimal hepatic metabolism; rather, it undergoes spontaneous hydrolysis to become active. It is primarily excreted by the kidneys via tubular filtration. The exposure to carboplatin is well characterized by its AUC, which is associated with its antineoplastic activity as well as toxicity. Carboplatin is much less toxic than cisplatin, but its dose limiting toxicity is myelosuppression (especially thrombocytopenia). An AUC of 4 to 7 has manageable myelosuppressive effects with desirable efficacy against malignant cancers. Since carboplatin is less nephrotoxic, neurotoxic and emetogenic than cisplatin, it can be an ideal agent for dose-intensive and/or combination chemotherapies.

Carboplatin was introduced in 1981 as a favorable alternative to cisplatin for the treatment of many solid tumors. Carboplatin is FDA approved for the initial or palliative (previously treated with cisplatin) treatment of advanced ovarian tumors when combined with other approved chemotherapy agents. Carboplatin is also used in a variety of malignancies such as ovarian cancer, bladder cancer, metastatic breast cancer, cervical cancer, esophageal cancer, head and neck cancer, lymphoma, lung cancer, unknown primary adenocarcinoma and testicular cancer.

Calvert Formula: ^{5-10, 13}

Most chemotherapy agents are dosed based on body surface area (BSA). However, this approach in the adult population often results in over- and under-dosing with carboplatin, since it does not take renal function variations into consideration. Carboplatin is preferred to be dosed based on renal function (i.e., glomerular filtration rate, GFR) in the adult and geriatric populations.

In 1989, Calvert and colleagues reported that pretreatment renal function is linearly related to carboplatin plasma clearance and strongly correlates with the severity of carboplatin-induced toxicities. A formula known as the “Calvert formula” was derived from a pharmacokinetic retrospective analysis of carboplatin in 18 patients. Subsequently, Calvert and colleagues refined the formula with additional prospective pharmacokinetic data. This formula is used to predict the dosage needed to achieve a desirable exposure of carboplatin (i.e., AUC) based on patient’s renal function (i.e., GFR). AUC values of 4 to 6 (for previously treated patients) and 6 to 8 (for treatment naïve patients) will give an acceptable hematological toxicity. By using a target AUC instead of a fixed dose, the exposure of carboplatin can be more consistent within the population. The final formula is simplified to:

Calvert formula: Dose=AUC x (GFR + 25)

The value of 25 mL/min is the constant used to correct for carboplatin non-renal clearance and irreversible binding to tissues.

Equation 1 shows the Calvert equation.

The Calvert formula has since been used in various studies. Van Warmerdam summarizes the findings from these studies: (1) toxicity increases with increasing AUC; (2) AUC is more closely related to toxicity and efficacy than the mg/m² dose; (3) the Calvert formula is suitable for a wide range of dosages (up to 2400 mg/m²); (4) Calvert formula remains accurate when carboplatin is combined with etoposide, bleomycin, cisplatin, cyclophosphamide and ifosfamide; (5) some patients may experience more toxicity than others at equivalent AUC values; this may be due to the recovery capacity of the bone marrow in individual patients.

The major component in the Calvert formula is GFR, thus directly measuring GFR (i.e., using radioactive injection of chromium-EDTA and taking at least three to five blood samples) will provide the most accurate GFR values. However, this assay is not available or practical in a clinical setting. An alternative is to estimate GFR by using creatinine clearance via a 24-h urine collection, or more conveniently, by calculating the GFR with serum creatinine (SCr) by using the Jelliffe, Cockcroft-Gault or Chatelut equations.

$$Cl_{\text{carbo}} = (0.134 \times \text{weight (kg)}) + ((1 \text{ if male, } 0.686 \text{ if female}) \times 218 \times \text{weight (kg)} \times (1 - (0.00457 \times \text{age (yrs)}))) / (\text{serum creatinine (mg/dl)} \times 88.4)$$

Equation 2 shows the Chatelut equation to estimate GFR.

$$CL_{\text{CR-Jelliffe}} \text{ (mL/min)} = \frac{98 - 16 \cdot \left[\frac{\text{age (y)} - 20}{20} \right]}{\text{Serum creatinine (mg/100 mL)} \cdot 0.9 \text{ (for female)}}$$

Equation 3 shows the Jelliffe equation.

Males	$\frac{\text{weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine}}$
Females	0.85 x above value

Equation 4 shows the Cockcroft-Gault equations to estimate GFR (SCr in mg/dL).

- The Cockcroft-Gault equation is generally preferred for nonelderly patients with normal SCr values; this equation is most commonly used.
- The Jelliffe equation may be preferred for men with elevated SCr (i.e., > 1.5 mg/dL)
- The Chatelut equation may be the most accurate but is more complex.
- If done correctly, all four methods (24-h urine collection, Cockcroft-Gault, Jelliffe and the Chatelut equations) all produce acceptable results in estimating creatinine clearance and thus GFR.

Dosing in Obese Patients: ¹⁰⁻¹¹

An accurate estimation of kidney function is essential for optimizing the carboplatin dosage to maximize efficacy and minimize toxicity. However, this is challenging in patients who are obese because the weight-based formula, like the Cockcroft-Gault equation, may overestimate the GFR. In a retrospective analysis of 20 overweight and obese patients, the use of actual body weight in the Cockcroft-Gault equation overestimated GFR and subsequently carboplatin dosing resulted in a higher incidence of toxicity (25 percent of patients experienced grade 3 or 4 thrombocytopenia, 10 percent had a treatment delay and 10 percent received a dose reduction due to toxicity).

Ekhart et al studied 240 cancer patients, seven who were underweight (BMI<18.5 kg/m²), 146 normal weight (BMI≥18.5 to <25), 72 overweight (BMI≥25 to <30) and 15 obese (BMI≥30). This study suggests that in overweight and obese patients, **adjusted ideal body weight** is the best weight descriptor to be used in Cockcroft-Gault equation. In addition, **lean body mass** is the best weight descriptor in underweight and normal weight patients. Interestingly, this study also concluded that in patients who are overweight or obese with a normal renal function a flat carboplatin dose results in less bias.

$$AIBW = IBW + 0.4 \times (ABW - IBW)$$

Equation 5 shows the adjusted ideal body weight formula.

New FDA Recommendations on Capping Parameters: ¹²

At the end of 2010, all U.S. clinical laboratories have changed to use the new standardized Isotope Dilution Mass Spectrometry (IDMS) method to measure SCr. This method appears to **underestimate SCr values** when they are relatively low (i.e., 0.7 mg/dL). Subsequently, this underestimation results in an overestimation of GFR. This overestimation will result in a higher than desired carboplatin dose and thus an increased risk of carboplatin-induced toxicity.

The National Cancer Institute/Cancer Therapy Evaluation Program and the FDA are recommending new capping parameters for calculating carboplatin dosages using the Calvert formula. If the patient's GFR is estimated based on SCr measurements by the IDMS method, then the maximum estimated GFR should be **capped at 125 mL/min**.

- Calvert formula: Total Carboplatin Dose (mg) = (target AUC) x (GFR +25) with (**Maximum GFR=125**)
- **Maximum Carboplatin Dose (mg)** = target AUC (mg·min/mL) x (**150 mL/min**)

Target AUC (mg·min/mL)	6	5	4
Maximum dose (mg)	900	750	600

Table 1 shows the target AUC and the corresponding maximum carboplatin dosage.

Seton Dosing Guidelines:

In summary, due to the recent changes in the SCr measurement, there has been a new recommendation for the maximum dosage of carboplatin. The Seton Healthcare Family is currently updating dosing guidelines to provide pharmacists with dosing parameters for carboplatin that will incorporate this new information.

References:

1. Carboplatin. Lexi Drugs Online [database online]. Lexi-Comp, Inc., Hudson, Ohio, USA. 1978-2012. Available at: <http://online.lexi.com>. Accessed on Feb. 25, 2012.
2. Carboplatin. MicroMedex 2.0 [database online]. Thomson MicroMedex, Greenwood Village, Colorado, USA. Available at: www.thomsonhc.com. Accessed on Feb. 25, 2012.
3. Carboplatin. Clinical Pharmacology [database online]. Tampa, Florida, USA: Gold Standard, Inc.; 2012. Available at: www.clinicalpharmacology.com. Accessed on Feb. 25, 2012.
4. Medina PJ, Shord SS. Chapter 135. Cancer Treatment and Chemotherapy. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, eds. *Pharmacotherapy: A Pathophysiologic Approach*. 8th ed. New York: McGraw-Hill; 2011. <http://www.accesspharmacy.com>. Accessed on Feb. 26, 2012.
5. Calvert AH, Newell DR, Gumbrell LA, et al. Carboplatin dosage: Prospective evaluation of a simple formula base on renal function. *Journal of Clinical Oncology*. 1989;1748-56.
6. van Warmerdam LJC, Rodenhuis S, ten Bokkel Huinink WW, et al. The use of the Calvert formula to determine the optimal carboplatin dosage. *J Cancer Res Clin Oncol*. 1995;121:478-86.
7. Alberts DS, Dorr RT. New perspective on an old friend: Optimizing carboplatin for the treatment of solid tumors. *The Oncologist*. 1998;3:15-34.
8. Mazumdar M, Smith A, Tong WP, et al. Brief Communications: Calvert's formula for dosing carboplatin: Overview and concerns of applicability in high-dose setting. *J Natl Cancer Inst*. 2000;92(17):1434-36.
9. Ando M, Minami H, Ando Y, et al. Multi-institutional validation study of carboplatin dosing formula using adjusted serum creatinine level. *Clin Cancer Res*. 2000;6:4733-38.
10. Nightingale G, Trovato JA, Lee M, et al. Carboplatin dosing in overweight and obese patients: A single-center experience. *J Hematol Oncol Pharm*. 2011;1(3):18-24.
11. Ekhart C, Rodenhuis S, Schellens JHM, et al. Carboplatin dosing in overweight and obese patients with normal renal function, does weight matter? *Cancer Chemother Pharmacol*. 2009;65:115-22.
12. Carboplatin Dosing. U.S. Food and Drug Administration. Available online at <http://www.fda.gov>. Accessed on Feb. 26, 2012.
13. Graphic for Figure 2. Available online at <http://www.nature.com/clpt/journal/v67/n6/full/clpt200065a.html>. Accessed Feb. 26, 2012.