

ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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Current Dilemmas in Carboplatin Dosing

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H&O Can you provide some background on carboplatin?

MR Carboplatin is a platinum chemotherapy drug that is administered as an intravenous infusion. It has a broad role in oncology, particularly in solid tumors. It is most commonly used to treat lung and ovarian cancers, but has been used off-label in many other diseases. Carboplatin is unique in oncology in that it is the only drug that is dosed based on estimation of renal function.

H&O What are the concerns associated with carboplatin dosing?

MR The main challenge in accurate carboplatin dosing is determining how to estimate renal function. The original studies that showed a relationship between renal function and carboplatin clearance used a radioisotope that had been rarely employed in clinical practice. A lot of the variability in calculating the carboplatin dose is due to physicians utilizing results of serum creatinine tests to estimate the glomerular filtration rate (GFR), as based on one of various formulas, many of which have not been sufficiently prospectively evaluated. The concern we face is that the historical approach has primarily relied on the creatinine measurement in the estimation of renal function. However, recent standardization of creatinine assays

has resulted in lower values for most patients. This leads to the potential overdose of patients, particularly those with normal renal function. Because of these challenges, questions arise as to what should be done by agencies like the US Food and Drug Administration (FDA) or the National Cancer Institute, or by pharmaceutical companies to combat this significant public health issue. Furthermore, what should the clinician do when treating a patient outside of a clinical study? Unfortunately, no one knows the answer to these questions because of the uncertainty over carboplatin dosing.

H&O What factors are considered when determining the dose of carboplatin?

MR When deciding what factors to incorporate into the calculation of carboplatin dosing, one generally utilizes existing clinical trial data that targeted a specific area under the concentration-time curve (AUC). The dose required to achieve the target AUC is then estimated based on one of the available formulas, ideally the one that was studied in the clinical trial that is being used as the basis for the treatment decision. These formulas typically include creatinine level, age, weight, and sex (Table 1). Other factors that may be considered include ethnicity and height. Different studies employ different formulas or approaches to carboplatin dosing. Currently, there is marked uncertainty as to what the “correct” formula is, but the immediate challenge is to avoid overdosing of patients with apparently normal renal function. Setting an upper limit on renal function may help avoid this problem.

Table 1. Formulas Used in Carboplatin Dosing

Formula	Variables used
Cockcroft-Gault formula	Uses age, weight, serum creatinine, and sex to determine creatinine clearance
Calvert formula	Uses AUC and GFR to determine dose
Calvert formula*	Modified to determine maximum carboplatin dose using target AUC (mg min/mL) \times 150 mL/min
MDRD formula	Uses serum creatinine, age, ethnicity, and sex to determine GFR
CKD-EPI GFR equation	Uses serum creatinine, sex, age, and ethnicity to determine eGFR

AUC=area under the concentration time curve; CKD-EPI=chronic kidney disease epidemiology collaboration; GFR=glomerular filtration rate; MDRD=modification of diet in renal disease; Scr=serum creatinine.

*The FDA recommends capping the dose of carboplatin if a patient's GFR is estimated using serum creatinine measurements by the isotope dilution mass spectrometry method. The GFR in the Calvert formula should not exceed 125 mL/min.

H&O What are the new changes in serum creatinine, and how might they affect carboplatin dosing?

MR Because of the potential safety issue with carboplatin dosing, all laboratories in the United States are now required to use a new standardized method to measure serum creatinine called isotope dilution mass spectrometry (IDMS). This method, however, underestimates serum creatinine values compared to previous approaches when serum creatinine values are low, at approximately 0.7 mg/dL. Measuring serum creatinine with the IDMS method may result in overestimation of the GFR in patients with normal renal function, and if the carboplatin dose is calculated based on this method, the dose may result in drug-related toxicities. As a temporary measure, it has been suggested that physicians limit the dose of carboplatin in order to avoid overdosing if they are using the IDMS method to measure serum creatinine. For patients with abnormal renal function, the usual formulas are less

likely to be problematic. The population that is at greatest risk for an overdose is the group of patients with normal renal function, especially since there is little evidence of the value of AUC formulas to estimate dosing.

H&O How can we overcome the challenges faced with carboplatin dosing?

MR It is necessary to establish a consistent approach to estimating creatinine clearance so that we can reduce variability across institutions and translate clinical trial results into clinical practice. Studies evaluating carboplatin dosing are also being encouraged to address the current issues faced with dosing this drug.

There is another formula for renal function that has been suggested to be more accurate—the modification of diet in renal disease (MDRD) formula. Unlike the other commonly used formulas (eg, Cockcroft-Gault, Jelliffe), it is based on the new creatinine assay. The most commonly used MDRD formula estimates GFR using 4 variables: serum creatinine, age, race, and gender. Currently, there is not much evidence for its utility in the context of carboplatin dosing. A recent study, reported in the *Clinical Journal of the American Society of Nephrology*, compared the MDRD formula to a new chronic kidney disease epidemiology collaboration (CKD-EPI) equation, which was developed by using data from numerous studies. In this study, the CKD-EPI equation was found to have better performance than the MDRD equation; however, further research is needed to determine if widespread use of CKD-EPI is appropriate.

Suggested Readings

- US Food and Drug Administration. Carboplatin dosing. <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm228974.htm>.
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- National Kidney Foundation. GFR calculator. http://www.kidney.org/professionals/KLS/gfr_calculator.cfm.
- National Kidney Disease Education Program. GFR MDRD Calculator for Adults. http://www.nkdep.nih.gov/professionals/gfr_calculators/idms_con.htm.