CLINICAL Q&A

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Carboplatin Dosing Accounting for the Renal and Hematologic Status of Patients

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Question: What is the appropriate way to dose carboplatin (Paraplatin®, Bristol-Myers Squibb, Princeton, NJ) when patients' creatinine clearance (CrCl) are decreased or a concern exists about patients' hematologic status (e.g., decreasing the dose after using a standard area under the curve [AUC] dosing or by choosing a lower AUC)?

Case study: A patient has received one cycle of a chemotherapy regimen that includes a carboplatin dose at an AUC of six. The patient experienced a prolonged nadir that caused the next cycle to be delayed by one week. The physician wishes to dose reduce for cycle two of the chemotherapy regimen. Should the new dose be calculated at an AUC of four or five or should the original AUC of six be arbitrarily reduced by 20%–25%?

Answer: Neither method alone would be appropriate as an adjustment for renal impairment; both would result in underdosing. These methods may be appropriate if based on toxicity from a previously administered dose or other factors such as prior chemotherapy, radiotherapy, or patient performance status. The manufacturer provides guidance on recommended dosage adjustments based on hematologic responses from a previously administered dose (Bristol-Myers Squibb, 2001) (see Table 1). These are derived from controlled trials and based on platelet or neutrophil count nadir.

For the case study in question, adjustment of the AUC to four would be a 33% reduction; an AUC of five would be a 17% reduction. Calculating dosage to the original AUC of six and then adjusting based on the hematologic nadir as per the guidelines would be an appropriate strategy. The oncologist empirically may choose to make further adjustments based on other patient factors such as severity and duration of nadir counts or a change in performance status. An understanding of the rationale behind AUC dosing of carboplatin is needed to properly determine patients' dosage requirements.

Area Under the Concentration Versus Time Curve

The pharmacokinetics of a drug can be illustrated graphically by plotting the serum drug concentration level versus time after drug administration. The shaded area in Figure 1 illustrates the AUC. The units in this example are mg/ml times minutes (i.e., area = length times width). This value is a measure of systemic drug exposure in patients. In the case of carboplatin, AUC is predictive of hematologic toxicity and optimal efficacy (Alberts & Dorr, 1998). A smaller relative dose would be required to achieve an equivalent AUC in the setting of patients with decreased drug clearance. In this case, the peak concentration would be lower but the time to elimination would be longer.

Formula Dosing of Carboplatin

Carboplatin is excreted principally in the urine. The rate of clearance is correlated closely with the glomerular filtration rate
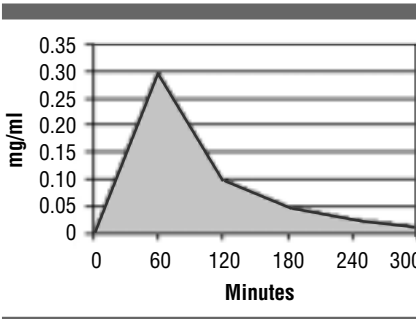

FIGURE 1. AREA UNDER THE CONCENTRATION VERSUS TIME CURVE

(GFR) or CrCl (McEvoy, 2001). Thus, the carboplatin AUC is related linearly to dose when allowance is made for variations in renal function (Calvert, Harland, Newell, Siddik, & Harrap, 1985). A formula has been devised to calculate the total dose of carboplatin at a predetermined AUC, with the dose in milligrams determined by the individual patient's GFR (Calvert et al., 1989). In the 1990s, AUC largely has replaced body surface area (BSA) as the basis for dosing carboplatin in clinical trials and clinical practice. Use of AUC-based formula dosing compensates for patient variations in pretreatment renal function that might otherwise result in underdosing, as in patients with above average renal function, or overdosing, as in patients with impaired renal function.

The formula-dosing method used most commonly in adults is the Calvert formula (total dose [mg] = target AUC x [GFR + 25]). This method appears in the U.S. Food and Drug Administration's prescribing information for Paraplatin (Bristol-Myers Squibb, 2001).

TABLE 1. PARAPLATIN® DOSAGE ADJUSTMENT GUIDELINES

PLATELET NADIR	NEUTROPHIL NADIR	ADJUSTED DOSE FROM PRIOR COURSE
> 100,000	> 2,000	125% (i.e., increase by 25%)
50,000–100,000	500–2,000	No adjustment
< 50,000	< 500	75% (i.e., decrease by 25%)

Note. Based on information from Bristol-Myers Squibb, 2001.

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