Carboplatin Dosing Accounting for the Renal and Hematologic Status of Patients

Tom Busse, PharmD

**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 (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).

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**Table 1. Paraplatin® Dosage Adjustment Guidelines**

<table>
<thead>
<tr>
<th>PLATELET NADIR</th>
<th>NEUTROPHIL NADIR</th>
<th>ADJUSTED DOSE FROM PRIOR COURSE</th>
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<tbody>
<tr>
<td>&gt; 100,000</td>
<td>&gt; 2,000</td>
<td>125% (i.e., increase by 25%)</td>
</tr>
<tr>
<td>50,000–100,000</td>
<td>500–2,000</td>
<td>No adjustment</td>
</tr>
<tr>
<td>&lt; 50,000</td>
<td>&lt; 500</td>
<td>75% (i.e., decrease by 25%)</td>
</tr>
</tbody>
</table>

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

**Figure 1. Area Under the Concentration Versus Time Curve**

Digital Object Identifier: 10.1188/03.CJON.104-108
Other formulas have been devised either as an alternative in adults (Huitema et al., 2001; Sculier et al., 1999) or for pediatric use (Solimando & Waddell, 2002). Discussion of these other methods is beyond the scope of this column.

**Determining the Glomerular Filtration Rate or Creatinine Clearance**

GFR, as used in the Calvert formula, is a measure of renal function and essentially is equivalent to CrCl. In developing the formula, Calvert et al. (1989) determined GFR using a radiopharmaceutical method. Determining GFR this way is expensive and inconvenient. Alternative methods to calculate GFR include a 24-hour urine collection for CrCl or the use of a variety of formulas to calculate an estimated CrCl. The use of estimated CrCl results in more complex dosage calculations may not be as accurate. Despite this, clinicians commonly estimate CrCl because it is the most convenient method (Waddell & Solimando, 2000). Variables introduced with the use of estimated CrCl include the following.

- **CrCl formula:** Several methods have been used. See Table 2 for examples. The Paraplatin prescribing information does not provide a specific formula. A slide-rule calculator distributed by the manufacturer uses the Jelliffe method adjusted for body weight (Jelliffe, 1973). A computer software calculator also from the manufacturer includes two additional methods: Jelliffe not adjusted for BSA and Cockcroft-Gault using ideal body weight (IBW) (Bristol Laboratories Oncology Products, 1997).

- **Serum creatinine (SCr):** Only relatively stable values will provide an accurate CrCl estimate. Abnormally low SCr may be unreliable in some patients (Waddell & Solimando, 2000). Variation has been noted depending on the methods used for determining SCr. The older laboratory method (i.e., Jaffe) reports slightly higher SCr than the newer enzymatic laboratory method. Research is not clear as to which method is more accurate for carboplatin dosing purposes (Leger et al., 2002; Waddell & Solimando).

- **Body weight:** Doses calculated using formulas that incorporate body weight or BSA are affected by this variable. Using actual body weight (ABW) versus IBW or adjusted body weight will yield different results when dosing obese patients. Actual weights tend to overestimate clearance whereas ideal weights tend to underestimate clearance in obese patients. The best strategy may be to use actual weight in calculations for most patients and use adjusted weight [IBW + 40% (ABW – IBW)] for morbid obesity (Benezet et al., 1997; Waddell & Solimando, 2000).

These factors can lead to variations of up to 40% between desired and achieved carboplatin AUC when using formula dosing. The use of BSA for calculating doses can lead to variations of 100%–300%. Thus, any method of AUC-based carboplatin dosing is more accurate than dosing according to BSA (Calvert et al., 1995).

**Summary**

Using AUC-based dosing compensates for variations in renal function between and within individual patients. It does not adjust for other factors such as previous chemotherapy, previous radiotherapy, or performance status. One empiric method to adjust for these factors would be reduction of the ideal AUC. However, because AUC-based dosing accounts for variations in renal function, this would not be an appropriate method to adjust dosing based solely on renal function changes.

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### References


### Table 2. Formulas for Computing Creatinine Clearance

<table>
<thead>
<tr>
<th>Method</th>
<th>Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cockcroft-Gault</td>
<td>( \frac{(140 – \text{age} \text{ (in kg)})}{(72 \times \text{SCr in mg/dl})} \times (0.85 \text{ if female}) )</td>
</tr>
<tr>
<td>Jelliffe</td>
<td>( \frac{98 – 0.8(\text{age in years} – 20)}{\text{SCr in mg/dl}} \times (0.9 \text{ if female}) )</td>
</tr>
<tr>
<td>Jelliffe (adjusted for body surface area [BSA])</td>
<td>( \frac{98 – 0.8(\text{age in years} – 20)}{\text{SCr in mg/dl}} \times \frac{\text{patient’s BSA}}{1.73 \text{ m}^2} \times (0.9 \text{ if female}) )</td>
</tr>
</tbody>
</table>

SCr—serum creatinine

Note. Based on information from Bristol Laboratories Oncology Products, 1997; Jelliffe, 1973.