Carboplatin has been approved by the US Food and Drug Administration for the treatment of ovarian cancer and has been used off-label for the treatment of many solid tumors, including lung, head and neck, endometrial, breast, and cervical cancers. As a nonclassical alkylating agent, carboplatin acts by covalently binding to DNA, thereby interfering with the cross-linking and synthesis of DNA and cell replication. Carboplatin is excreted almost exclusively by the kidneys. Approximately 65% to 70% of the total platinum dose is eliminated as intact carboplatin in the urine during the first 12 to 16 hours after administration.

Carboplatin dosage relies on glomerular filtration rate (GFR) and area under the curve (AUC). The

**Background:** Serum creatinine–based formulas are used to estimate glomerular filtration rate when calculating carboplatin dosage with the Calvert formula. In overweight and obese patients, body weight applied to serum creatinine–based formulas may overestimate glomerular filtration rate. Overestimation may result in divergent carboplatin dosages that correlate with dose-limiting thrombocytopenia, treatment delays, and dose reductions.

**Objective:** The primary objective of this study was to evaluate physician prescribing practices with the Calvert formula in overweight and obese patients. The secondary objective was to identify presence of grade 3 or 4 thrombocytopenia, per the National Cancer Institute Common Toxicity Criteria for Adverse Events, treatment delays, and dose reductions.

**Method:** A retrospective analysis was conducted using data from a total of 20 patients who received carboplatin therapy. Adults who received at least 1 dose of carboplatin with documentation of desired area under the concentration-time curve were included. Patients were excluded if baseline laboratory values were not available. We identified the serum creatinine–based formula utilized, the body weight descriptor applied to the glomerular filtration rate formula, and whether a maximal/capped creatinine clearance rate was determined.

**Results:** A total of 50 patients were screened for eligibility, and 20 were included in the final analysis. Prescribers utilized the Cockcroft-Gault formula to estimate glomerular filtration rate in 100% of the participants (N = 20). Actual body weight was applied in 95% (N = 19) of the patients. Twenty-five percent of the patients (N = 5) experienced grade 3 or 4 thrombocytopenia, 10% (N = 2) experienced a carboplatin treatment delay, and 10% (N = 2) had a documented carboplatin dose reduction secondary to toxicity.

**Conclusion:** The use of actual body weight in the Cockcroft-Gault equation to estimate glomerular filtration rate in the Calvert formula was associated with a high percentage of adverse clinical events. Increased awareness is needed in the oncology community to highlight unique considerations and confirm quality assurance when estimating renal clearance in the Calvert formula in overweight and obese patients. Prospective studies are needed to substantiate these preliminary clinical data.
Carboplatin Dosing in Overweight and Obese Patients

Carboplatin Dosing in Overweight and Obese Patients

Calvert formula is the preferred method to calculate the dose for a given target AUC. Serum creatinine (SCr)-based formulas are used to estimate GFR when calculating carboplatin dosage with the Calvert formula. Individualized dosing is the current practice to control plasma drug exposure of carboplatin. A limitation of the Calvert formula is that the carboplatin dosage can substantially vary, depending on the SCr-based formula used to estimate GFR (ie, Cockcroft-Gault, Jelliffe, or Modification of Diet in Renal Disease [MDRD]).

Furthermore, in overweight and obese populations, body weight applied to a SCr-based formula may overestimate GFR. Overestimation of GFR may result in differences in carboplatin dosage that correlate with clinically relevant events. A study by Herrington and colleagues demonstrated that the optimal weight for overweight and obese patients in SCr-based formulas for use in the Calvert formula was adjusted body weight. The use of actual body weight in overweight or obese patients resulted in a carboplatin AUC that was 30% to 40% higher than the predicted or targeted carboplatin AUC.

Table 1 Serum Creatinine–Based Formulas

<table>
<thead>
<tr>
<th>Formula</th>
<th>Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calvert formula&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Carboplatin total dose, mg = target AUC, mg/mL•min × (GFR, mL/min + 25)</td>
</tr>
<tr>
<td>Original Cockcroft-Gault&lt;sup&gt;b&lt;/sup&gt;</td>
<td>CrCl, mL/min = ([140 – age, y] × [actual body weight, kg]) ÷ [72 × SCr, mg/dL] Females: multiply above result by 0.85</td>
</tr>
<tr>
<td>Modification of Diet in Renal Disease&lt;sup&gt;c&lt;/sup&gt;</td>
<td>GFR (mL/min/1.73 m&lt;sup&gt;2&lt;/sup&gt;) = 170 × [SCr (mg/dL)]&lt;sup&gt;–0.999&lt;/sup&gt; × [age, y]&lt;sup&gt;–0.176&lt;/sup&gt; × [0.762 if patient is female] × [1.180 if patient is black] × [BUN, mg/dL]&lt;sup&gt;–0.170&lt;/sup&gt; × [albumin, g/dL]&lt;sup&gt;–0.318&lt;/sup&gt;</td>
</tr>
<tr>
<td>Jelliffe equation&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Males: CrCl (mL/min/1.73 m&lt;sup&gt;2&lt;/sup&gt;) = (98 – [0.8 × [age, y – 20]]) + SCr, mg/dL Females: multiply above result by 0.9</td>
</tr>
<tr>
<td>Ideal body weight</td>
<td>Males: 50 kg + 2.3 × (height, in – 60) Females: 45.5 kg + 2.3 × (height, in – 60)</td>
</tr>
<tr>
<td>Adjusted body weight</td>
<td>Adjusted body weight (kg) = ideal body weight + [0.4 × (actual body weight, kg – ideal body weight, kg)]</td>
</tr>
</tbody>
</table>


AUC indicates area under the curve; BUN, blood urea nitrogen; CrCl, creatinine clearance; GFR, glomerular filtration rate; SCr, serum creatinine.

In overweight and obese populations, body weight applied to a SCr-based formula may overestimate GFR. Overestimation of GFR may result in differences in carboplatin dosage that correlate with clinically relevant events.

Study Objectives

The primary objective of this retrospective analysis was to evaluate physician prescribing practices with the Calvert formula in overweight and obese patients within our institution. Specifically, we identified the SCr-based formula used by the physician prescriber to estimate the GFR and body weight (ie, actual, ideal, adjusted) applied to the SCr-based formula, and whether a maximal/capped creatinine clearance (CrCl) rate was determined at the discretion of the prescriber. This information was gathered from a preprinted
chemotherapy order form that included calculations for estimated renal function and the body weight descriptor applied. The secondary objectives were to identify the presence of grade 3 or 4 thrombocytopenia (25.0–49.9 × 10⁹/L or <25 × 10⁹/L) according to the National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events, dose modifications, and treatment delays caused by toxicity.

Methods
This study was reviewed and approved by the University of Maryland Institutional Review Board. A retrospective analysis was conducted using data from patients who received carboplatin therapy during the period between January 2008 and January 2009. Inclusion criteria were adult patients (aged ≥18 years) who received at least 1 dose of carboplatin with documentation of desired carboplatin AUC for solid tumor malignancies either as monotherapy or as part of combination chemotherapy treatment. Exclusion criteria included patients with incomplete or missing laboratory parameters on the preprinted chemotherapy order form. Patient data were accessed through electronic medical records. Data collection included demographic information, pretreatment and posttreatment complete blood count and nadir, concurrent cytotoxic chemotherapy, and any supporting documentation confirming treatment delays and dose reductions.

We defined treatment delays as ≥7 days from the planned day of carboplatin administration. A dose reduction was defined as a ≥20% dose decline or a reduction in the target AUC from the previous dose, with supporting documentation on the chemotherapy order confirming a dose reduction secondary to toxicity.

The actual carboplatin AUC and actual GFR were not measured as part of this analysis. Stable kidney function was defined by SCr change from baseline of <0.5 mg/dL. The SCr-based formula utilized by the prescribing physician, the body weight applied to the formula, the target AUC, and the treatment cycle number were collected from the chemotherapy order. Patients were categorized based on actual body weight (kg) and height (cm) into 1 of 5 groups, including:

- Low body weight: body mass index (BMI) <18.5 kg/m²
- Normal/ideal body weight: BMI 18.5-24.9 kg/m²
- Overweight: BMI 25-29.9 kg/m²
- Obese class I: BMI 30-34.9 kg/m²
- Obese class II: BMI 35-39.9 kg/m²
- Extreme obesity/class III: BMI >40 kg/m².

Body weight categories are based on the National Institutes of Health guidelines on the identification of overweight and obese adults. Study analysis for end points included overweight, obese, and extremely obese patients.
Results

A sample of 50 patients who received carboplatin during the study period were screened for eligibility, and more than 10 medical oncology prescribers dosed carboplatin with the Calvert formula. Thirty patients were excluded based on criteria for low body weight, ideal body weight, or missing laboratory parameters; therefore, 20 patients were included in the final analysis (Figure).

The demographics and baseline laboratory values of the patients are described in Table 2. The study demographics included mean age of 62.3 years, and more whites than blacks comprised the study population.

Most patients had a primary diagnosis of non–small-cell lung cancer, followed by malignancy of the head and neck.

Fifty percent of the patients were obese, and the mean BMI was 32.059 kg/m².

Based on the target carboplatin AUC, more than two thirds of patients were prescribed a carboplatin target AUC ≥5 mg/mL/min. Kidney function was stable for all patients.

Seventy percent of the patients (N = 14) were treated with doublet-combination chemotherapy, and the remaining 30% of patients (N = 6) received a triple-combination chemotherapy regimen. The doublet-combination regimens included paclitaxel (N = 8), gemcitabine (N = 3), pemetrexed (N = 2), and etoposide (N = 1). The triple-combination chemotherapy regimens included paclitaxel (N = 5) and gemcitabine (N = 1) to monoclonal antibodies such as bevacizumab, cetuximab, and an investigational agent.

Physician prescribers used the Cockcroft-Gault formula to estimate GFR for use in the Calvert formula in 100% of the patients (N = 20). Prescribers applied the laboratory-derived SCr to all SCr-based formulas. Prescribers did not apply an adjusted SCr value to account for the influence of muscle mass on creatinine concentrations in the elderly.

Actual body weight was applied to the SCr-based formula in 19 patients (95%). Mean body weight was applied to the SCr-based formula in 1 patient. Of note, this patient was extremely obese with a BMI of 48.5 kg/m².

A maximum/capped CrCl rate of 125 mL/min was used for 2 patients (10%). Both of these patients had calculated GFR estimates of >150 mL/min based on the Cockcroft-Gault formula, and these patients were enrolled in clinical protocols with amendments for capping CrCl rates.

Five patients (25%) experienced grade 3 or 4 thrombocytopenia, 2 patients (10%) experienced a carboplatin treatment delay secondary to toxicity, and these 2 patients subsequently were discontinued from treatment with carboplatin.

In addition, 2 patients (10%) had a documented carboplatin dose reduction secondary to grade 3 or 4 thrombocytopenia. Overall, there were 9 documented clinical events occurring in 5 (25%) of the patients (Table 3).

Discussion

An accurate assessment of kidney function is necessary and vital for determination or modification of dosages of chemotherapy agents eliminated through the kidney in an effort to minimize toxicity and maximize efficacy.

Table 2. Baseline Characteristics of 20 Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean ± SD</td>
<td>62.30 ± 10.06</td>
</tr>
<tr>
<td>Sex, N (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>9 (45)</td>
</tr>
<tr>
<td>Female</td>
<td>11 (55)</td>
</tr>
<tr>
<td>Race, N (%)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>13 (65)</td>
</tr>
<tr>
<td>Black</td>
<td>7 (35)</td>
</tr>
<tr>
<td>Other</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Cancer, N (%)</td>
<td></td>
</tr>
<tr>
<td>Lung cancer</td>
<td>14 (70)</td>
</tr>
<tr>
<td>Head/neck cancer</td>
<td>3 (15)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Targeted carboplatin AUC, N (%)</td>
<td></td>
</tr>
<tr>
<td>2-4 mg/mL/min</td>
<td>7 (35)</td>
</tr>
<tr>
<td>5-7 mg/mL/min</td>
<td>13 (65)</td>
</tr>
<tr>
<td>Actual body weight, kg, mean ± SD</td>
<td>91.44 ± 17.29</td>
</tr>
<tr>
<td>Serum creatinine, mg/dL, mean ± SD</td>
<td>0.99 ± 0.00</td>
</tr>
<tr>
<td>Platelets, 10⁶/L, mean ± SD</td>
<td>282.15 ± 84.54</td>
</tr>
</tbody>
</table>

AUC indicates area under the curve; SD, standard deviation.
aminetetraacetic acid ($^{51}$Cr-EDTA) was originally used for the determination of the GFR in the Calvert formula.\(^2\) This method is costly and may be clinically impractical; therefore, GFR is usually estimated from SCr-based formulas.\(^{10-12}\)

Although these formulas are convenient to use, and they conserve time, there is a trade-off in accuracy and consistency with regard to the determination of GFR. The literature is limited in terms of guiding decision-making within the oncology community for addressing the influential variables within the Calvert formula in overweight and obese patients.

Our results demonstrate that physician prescribers utilized the Cockcroft-Gault equation to estimate GFR in all patients. None of our prescribers utilized the MDRD or the Jelliffe formula to estimate GFR. MDRD or the Jelliffe formula to estimate GFR. The Jelliffe equation is used by most gynecologic oncology group protocols, and gynecologic malignancies did not comprise our study population, which explains why the equation may not have been used.

Existing data comparing the Cockcroft-Gault equation and the MDRD equation for calculating estimated renal function in the Calvert formula were recently published. Shord and colleagues conducted a retrospective analysis to determine the absolute difference between the dose of carboplatin administered using traditional SCr-based formulas to estimate GFR versus the dose calculated based on the MDRD equation.\(^13\) Results showed a carboplatin AUC dose divergence in 48% of the patients, yet the frequency of neutropenia, thrombocytopenia, and dose modifications were similar between the 2 groups using either the SCr-based formulas or the MDRD equation to estimate GFR value. The investigators concluded that the traditional SCr-based formulas used to calculate carboplatin dosage should be used until more data become available regarding the use of the MDRD equation in this population.\(^13\)

The study conclusions are limited, because the goal was not specifically to evaluate dose divergence and clin-
ical outcomes in overweight and obese patients, but the study does provide some data regarding surrogate markers within the Calvert formula.

The NCI’s Cancer Therapy Evaluation Program released 2 action letters in October 2010 to address carboplatin dosing on sponsored protocols and the recent increase in toxicity.14,15 The program recommends utilizing the Cockcroft-Gault equation for calculating CrCl, and commented that the GFR used in the Calvert formula to calculate AUC-based dosing should not exceed 125 mL/min, in an attempt to prevent the erroneous overprediction of renal function estimates when using actual weight in the Cockcroft-Gault equation.

These initiatives are limited, because they do not address the body weight that should be applied to the Cockcroft-Gault equation in special populations of overweight and obese patients. Our prescribers applied actual body weight to the Cockcroft-Gault SCr-based formula in 95% of patients. In our study, applying actual body weight to estimate GFR for use in the Calvert formula did correlate with a high percentage of clinical events, including grade 3 or 4 thrombocytopenia and dose reductions secondary to toxicity.

The study by Herrington and colleagues demonstrated that the optimal weight to use for obese patients, defined as a BMI >30 kg/m2 with renal function and SCr within normal limits, was adjusted body weight.3 Using actual body weight in SCr-based formulas for the Calvert formula resulted in carboplatin AUCs 30% to 40% higher than predicted or targeted AUCs.3 The study results are limited because, despite evaluating actual versus targeted carboplatin AUC divergence in overweight and obese patients, the investigators did not objectively evaluate the impact of a supratherapeutic carboplatin AUC on clinical outcomes, such as dose-limiting myelosuppression or treatment delays.3

Ekhart and colleagues assessed the utility of alternative weight descriptors in the Cockcroft-Gault equation to more accurately predict carboplatin clearance in special body weight populations.5 The results demonstrated that adjusted body weight was the best weight descriptor in overweight and obese patients. The study results suggested that overweight and obese patients with normal renal function should receive a flat carboplatin dose based on population carboplatin clearance.

Existing data suggest a strong correlation between carboplatin AUC and dose-limiting myelosuppression, specifically thrombocytopenia.6-18 The incidence of thrombocytopenia in our study population was higher compared with those of standard populations. Based on data from Jodrell and colleagues in patients with ovarian cancer, the expected incidence of grade 3 thrombocytopenia for carboplatin AUC 4 to 5 is 5%, AUC 5 to 6 is 10%, and AUC 6 to 7 is 20%.19

Limitations
There are some limitations to our investigation. This was a retrospective study design, and we were not able to control for the heterogeneity that comprised our small study population.

There was also inconsistency with regard to the number of carboplatin treatment cycles that patients received in relation to documented dose reductions or treatment delays.

Inconsistency also occurred with the time at which the complete blood count and nadir(s) were taken and evaluated for each patient. The chemotherapy combination regimens that each patient received were not well balanced, thus the addition of other cytotoxic chemotherapy agents, such as paclitaxel, increases the risk and severity of myelosuppression when compared with monotherapy. We did not identify any independent risk factors predicting dose reductions or therapy delays resulting from toxicity (ie, race, sex, age, cancer diagnosis, baseline platelet count, and previous myelotoxic chemotherapy, concurrent radiation therapy, or performance status).

Finally, we did not measure actual carboplatin AUC or actual GFR utilizing 51Cr-EDTA.

Our results contribute to existing data regarding prescribing patterns within our institution and highlight unique considerations when calculating carboplatin dosage with the Calvert formula in overweight and obese patients.

Conclusion
Despite the study limitations, our results contribute to existing data regarding prescribing patterns within our institution and highlight unique considerations when calculating carboplatin dosage with the Calvert formula in overweight and obese patients. The use of actual body weight to estimate GFR in relation to the Calvert formula was associated with a high percentage of adverse clinical events.

Increased awareness and education regarding unique considerations with the Calvert formula in overweight and obese populations should be directed to medical oncology physician prescribers, pharmacists, and healthcare providers within the oncology community to establish quality assurance within the institution or practice site.

Future considerations include designing a prospective study evaluating body weight descriptors (ideal vs
adjusted) to estimate GFR for use in the Calvert formula incorporating measured carboplatin AUCs compared with target AUCs to identify dose divergence and subsequent adverse clinical events in this population. A prospective study may substantiate these preliminary, clinically relevant data and may be able to establish a consensus in clinical practice, which is critical for patient safety and clinical outcomes.

Author Disclosure Statement

Drs Nightingale, Trovato, Lee, and Thompson have reported no actual or potential conflicts of interest.

References