Measured versus estimated glomerular filtration rate in the Calvert equation: influence on carboplatin dosing

Abstract Purpose: Carboplatin is frequently dosed to achieve a desired area under the plasma concentration-time curve (AUC) by using the Calvert or Chatelut equations to estimate carboplatin clearance. Accurate determination of glomerular filtration rate (GFR) is necessary to correctly calculate carboplatin clearance using the Calvert equation. In clinical practice, the Cockcroft-Gault formula is frequently used to estimate GFR, but this practice has been reported to under- and overestimate carboplatin clearance. The purpose of this trial was to compare determinations of carboplatin clearance using the Chatelut equation and four separate GFR determinations, including $^{99m}$Tc-DTPA, the Cockcroft-Gault formula, a 24-h urine collection and a 2-h urine collection. Methods: Carboplatin clearance was estimated in 21 previously untreated extensive-stage small-cell lung cancer patients. GFR was determined using $^{99m}$Tc-DTPA, the Cockcroft-Gault formula, 24-h urine collection and 2-h urine collection. Serum and urine creatinine concentrations were measured using enzymatic assays. The carboplatin clearance was then calculated by individually adding 25 to the four GFR determinations based on the Calvert equation, which states that carboplatin clearance equals GFR + 25 (nonrenal clearance). The carboplatin clearance was also estimated using the Chatelut equation. The five determinations of carboplatin clearance were compared using Friedman’s test and post-hoc Wilcoxon signed rank tests. Precision and bias for each carboplatin clearance determination were calculated assuming that $^{99m}$Tc-DTPA provided the most accurate measure of GFR. Results: A statistically significant difference was found between the five methods of estimating carboplatin clearance ($P < 0.001$). No difference was found between carboplatin clearance calculated using $^{99m}$Tc-DTPA and the Cockcroft-Gault formula or the 2-h urine collection. The Chatelut equation provided more precision and less bias than the 2-h urine collection (median precision $20\%$ and $30\%$, median bias $-1\%$ and $-18\%$, respectively). Conclusion: Compared to $^{99m}$Tc-DTPA, the Chatelut equation more accurately estimates carboplatin clearance than the Cockcroft-Gault formula, the 2-h urine collection and the 24-h urine collection. The greater negative bias found for the latter three estimates of carboplatin clearance could result in underdosing of carboplatin.

Key words Carboplatin · Glomerular filtration rate · Creatinine clearance · Antineoplastic agents · Dosing

Introduction

Carboplatin is a frequently used antineoplastic agent with documented activity against a broad range of tumors [4, 14, 17, 29, 32, 38]. Carboplatin is dosed to achieve a targeted area under the concentration time curve (AUC) more commonly than the traditional dosing strategy based on body surface area [14]. This approach is supported by the relationship between carboplatin AUC and toxicity, specifically thrombocytopenia and neutropenia [5, 15, 16, 19, 24, 26, 34, 39]. In ovarian cancer patients, increased response rates are noted with increasing carboplatin AUC up to a plateau of 5–7 mg/min/ml [21]. In addition, treatment failures occur more frequently in patients with nonseminomatous germ cell tumors who have a carboplatin AUC less than 5 mg-min/ml [11, 20, 31]. These facts, combined with considerable interindividual variability in carbopl-
atin clearance, have led to the standard practice of
dosing carboplatin based on the desired AUC.

Since the carboplatin dose is calculated by multiply-
ing the target AUC by carboplatin clearance (carbo-
platin dose = AUC(times carboplatin clearance), an
accurate estimate of carboplatin clearance is essential.
Glomerular filtration rate (GFR), measured in terms of
$^{51}$chromium edathamil ($^{51}$Cr-EDTA) clearance, corre-
lates well with carboplatin clearance ($r^2 = 0.79–0.81$),
since carboplatin is mostly (50–70%) excreted un-
changed into the urine [9, 15, 39, 40, 44, 46]. Carboplatin
clearance can be estimated using methods developed by
Egorin et al., Calvert et al. and Chatelut et al., which
incorporate GFR estimations and other covariates [5, 9,
16]. In clinical practice, carboplatin clearance is com-
monly calculated by adding the patient’s GFR to 25
(nonrenal clearance based on the Calvert equation
(carboplatin dose = AUC(times GFR + 25)) [5].
The Calvert equation has been validated using
$^{51}$Cr-EDTA clearance to measure GFR, since $^{51}$Cr-
EDTA is highly correlated ($r^2 = 0.78$) with carboplatin
clearance [5]. Technetium-99m diethylene triamine pen-
taacetic acid ($^{99m}$Tc-DTPA) clearance can also provide
an unbiased estimate of carboplatin clearance when it is
used to measure GFR [27].

The use of these accurate radionuclide methods is
unfortunately limited by their inconvenience and
expense. In clinical practice, GFR is often estimated by
calculating creatinine clearance (CrCl) using the Cock-
croft-Gault formula [13]. Available data show that using
the Cockcroft-Gault formula to estimate GFR can lead
to either an underestimate [6, 7, 8, 9, 10, 23] or an
overestimate [1, 18, 28, 30] of carboplatin clearance.
Therefore, the use of this estimate may lead to inaccu-
racies in dosing of carboplatin.

The objectives of this trial were to (1) compare three
estimates of CrCl determined using a 2-h urine collec-
tion, a 24-h urine collection and the Cockcroft-Gault
formula with $^{99m}$Tc-DTPA, and (2) compare carboplatin
clearance calculated using the Chatelut equation [9], and
the four GFR determinations (i.e. $^{99m}$Tc-DTPA, 2-h
urine collection, 24-h urine collection and the Cockroft-
Gault formula).

### Patients and methods

Patient characteristics and chemotherapy regimen

The demographic characteristics of the study population are shown
in Table 1. Enrolled into a phase I study evaluating carboplatin,
topotecan and etoposide were 21 patients with previously untreated
extensive-stage small-cell lung cancer. The protocol was approved
by the Institutional Review Board at the University of North
Carolina and written informed consent was obtained for each
patient prior to study conduct. The patients were admitted to the
General Clinical Research Center (GCRC) at University of North
Carolina (UNC) Hospitals to receive their first cycle of chemother-
apy. Inclusion criteria included an ECOG performance status
of 0 to 2, serum creatinine <1.0 g/dl or CrCl >40 ml/min (based on
the Cockroft-Gault formula), and liver function tests less than

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patient characteristics*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>21</td>
</tr>
<tr>
<td>Men</td>
<td>12</td>
</tr>
<tr>
<td>Age (years)</td>
<td>Median 66, Range 44–77</td>
</tr>
<tr>
<td>Body weight, actual (kg)</td>
<td>Median 67, Range 45–104</td>
</tr>
<tr>
<td>Body weight, as percent of ideal</td>
<td>Median 109, Range 83–169</td>
</tr>
<tr>
<td>Body surface area (m$^2$)</td>
<td>Median 1.7, Range 1.4–2.3</td>
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<tr>
<td>Serum creatinine (mg/dl)</td>
<td>Median 0.8, Range 0.4–1.4</td>
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<tr>
<td>CrCl – Cockcroft-Gault (ml/min)</td>
<td>Median 90, Range 41–172</td>
</tr>
<tr>
<td>Carboplatin dose (mg)</td>
<td>Median 575, Range 328–985</td>
</tr>
</tbody>
</table>

three times the upper limit of normal. Patients were excluded if they
had received prior chemotherapy or radiation therapy or had had a
concurrent or previous malignancy within the previous 5 years.
None of the patients had preexisting kidney disease or renal
metastases. A standard diet was maintained throughout the study
and none of the patients received medications known to inhibit
renal tubular secretion (e.g. trimethoprim, cimetidine) or to cause
nephrotoxicity (e.g. aminoglycosides).

All patients received combination chemotherapy with carboplatin,
topotecan and etoposide. Carboplatin was dosed to a target
AUC of 5 mg·min/ml and administered as a 30-min intravenous
(i.v.) infusion. The actual administered carboplatin dose (in milligrams) was calculated using the Calvert equation as
5 × (GFR + 25). The Cockcroft-Gault formula was used to esti-
mate the GFR.

The first cohort ($n=6$) received carboplatin on day 1 of the
chemotherapy cycle. The remaining patients ($n=15$) received
carboplatin on the last day of i.v. chemotherapy, because patients in the first cohort developed dose-limiting toxicities. The first 15
patients received an 8-day regimen: carboplatin; topotecan i.v.
targeted to a lactone AUC of 15, 30 or 45 ng·h/ml over 30 min,
days 1–5; and oral etoposide 100 mg/m$^2$ per day, days 6–8.
Subsequent patients received the same chemotherapy regimen with
the duration of topotecan reduced to 3 days.

Estimates of GFR and carboplatin clearance

GFR was determined during the first chemotherapy cycle using
four different methods ($^{99m}$Tc-DTPA, the Cockcroft-Gault, 2-h
urine collection, and 24-h urine collection).

$^{99m}$Tc-DTPA clearance On day 2 of cycle one, patients received 3 mcg $^{99m}$Tc-DTPA i.v. and blood samples were obtained at
1 and 3 h after administration [35, 36]. $^{99m}$Tc-DTPA is the radio-
isotope routinely used to measure GFR at this hospital. The blood
samples were centrifuged in Amicon Centriffree filters and the ra-
dioactivity was counted. The data were fitted to a validated two-
compartment model and the plasma clearance of $^{99m}$Tc-DTPA was
calculated according to previously published methods [35, 36].

$^{99m}$Tc-DTPA plasma clearance is highly correlated ($r=0.97$) with
$^{51}$Cr-EDTA clearance, which has been shown to be correlated with
carboplatin clearance in a number of clinical trials [5, 9, 27, 39].
Carboplatin clearance was estimated by adding the $^{99m}$Tc-DTPA
plasma clearance to 25 (nonrenal clearance) based on the Calvert equation.