Evaluation of carboplatin dosing in non-small cell lung carcinoma patients using Calvert formula and Cockroft and Gault equation for glomerular filtration rate estimation

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Abstract. The aim of this study was to evaluate the reliability of the Cockroft and Gault (CG) equation for glomerular filtration rate (GFR) estimation in carboplatin dosing based on the Calvert formula. The records of 117 patients with advanced non-small cell lung carcinoma treated with carboplatin were retrospectively analyzed. Theoretical carboplatin doses derived from the Calvert formula using the CG equation were calculated for each chemotherapy cycle. Fluctuations in the theoretical carboplatin doses were analyzed, and discrepancies between actual carboplatin doses prescribed by the physician and theoretical doses were assessed. It was found that, compared with the first-cycle dose, subsequent theoretical doses were more than 10% higher in 79/320 cycles (24.7%) and more than 10% lower in 53/320 cycles (16.6%; P=0.015). A body mass index greater than or equal to 30 was associated with a tendency for increased CG-estimated GFR during subsequent chemotherapy cycles (P=0.009). Physicians tended to lower the prescribed dose (32.2% of the cycles) by using a higher serum creatinine (Scr) level for dose calculation than was actually measured. We concluded that Calvert formula-derived carboplatin doses fluctuate widely during repeated cycles when actual Scr is used for CG-estimated GFR. The measurement of 24-h creatinine clearance is advised as an alternative in selected patients with reduction in serum creatinine observed during treatments.

Introduction

An accurate assessment of renal function is essential for cancer patients receiving cytotoxic agents, which are primarily eliminated through the kidney in an unchanged form. Among these drugs is carboplatin, for which dosing is based on renal function rather than on body surface area (BSA) and is calculated using the Calvert formula: dose (mg) = AUC (GFR + 25) (1). Most protocols use an estimated glomerular filtration rate (eGFR), which is calculated using the Cockroft-Gault equation (CG), based on the serum creatinine (Scr) level, age and weight (2). Targeting the carboplatin dose based on the AUC leads to more predictable toxicity compared with dose determination based on BSA. However, CG may be unreliable in cancer patients due to confounding factors such as muscle mass, rate of metabolism of the muscle protein creatine to creatinine, absorption of dietary creatine, filtration of creatinine by the renal glomeruls and its secretion by the proximal renal tubules (3). In particular, the blood creatinine level may decrease in patients with advanced cancer due to a reduction of muscle mass, leading to false increases in the CG eGFR and, therefore, to unjustified increases in carboplatin dosing calculated according to the Calvert formula.

We hypothesized that the CG eGFR may be higher than the actual GFR in a considerable number of patients with advanced non-small cell lung carcinoma (NSCLC) treated with carboplatin, potentially leading to carboplatin overdosing. To test this hypothesis, fluctuations in Scr level, CG eGFR and the theoretical carboplatin dose derived from the Calvert formula, and CG eGFR based on actual Scr were retrospectively analyzed in repeated cycles of carboplatin-based chemotherapy in patients with advanced NSCLC. In addition, the dose of carboplatin resulting from the Calvert formula and the recent Scr was compared with the actual carboplatin dose prescribed by the physicians.

Materials and methods

Patients. Following approval of the study protocol by the institutional ethics committee, a retrospective analysis of all medical records of adult patients treated for advanced NSCLC in the Division of Oncology at Rambam Health Care Campus (RHCC), Haifa, Israel, between January 2007 and June 2010 was undertaken. Patients who had been treated with a carboplatin-based combination as first-line chemotherapy treatment were eligible for the study if they had received at least two cycles of carboplatin-containing combinations. Patients with elevated pretreatment Scr (i.e., >1.3 mg/dl) were excluded.

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Patient data recorded included gender, age, weight, height, NSCLC histological subtype, ECOG performance status (PS), disease stage, type of chemotherapy combination and Scr and blood urea nitrogen, which were routinely recorded prior to each chemotherapy cycle. Since malnutrition could be associated with decreased creatinine production, the body mass index (BMI) was calculated using the body weight measured at the beginning of the first cycle of carboplatin. Patients were classified as underweight, healthy weight, overweight or obese, according to the criteria of the Centers for Disease Control and Prevention (4).

Treatment. Three different carboplatin-based regimens were used: i) carboplatin (AUC5) and pemetrexed 500 mg/m^2, administered intravenously on day 1 every 21 days; ii) carboplatin (AUC6) and paclitaxel 200 mg/m^2, administered intravenously on day 1 every 21 days; and iii) carboplatin (AUC5) administered intravenously on day 1 and gemcitabine 1,000 mg/m^2 administered intravenously on days 1 and 8, with cycles repeated every 21 days.

The eGFR was calculated at the beginning of each cycle according to the CG formula: 140 - age (yrs) x body weight (kg) / 72 x Scr (mg/dl) (for females: x 0.85) (2). Scr is routinely determined in our center before each dose of carboplatin, and the relevant Scr was used for GFR calculation.

Renal function was graded in accordance with clinical practice guidelines published by the working group of the National Kidney Foundation (5): Stage 1, GFR ≥90 ml/min; Stage 2, GFR 60-89 ml/min; Stage 3, GFR 30-59 ml/min; Stage 4, GFR 15-29 ml/min; and Stage 5, GFR <15 ml/min.

Patient data, including body weight at the beginning of each chemotherapy line and Scr level at the beginning of each carboplatin-containing cycle, are routinely introduced into a computerized system used at our center (Prometheus), and the carboplatin dose, based on the Calvert formula and the CG equation, is routinely computed by that system. The maximal doses of carboplatin prescribed by the computerized system were those defined by the treatment protocol. The dose could be reduced at the discretion of the physician, who could determine that less than 100% of the dose would be prescribed. Moreover, the physician could further reduce the dose by inputting an Scr level higher than that measured prior to the relevant cycle. Modifications of the Scr were made at the physician's discretion and were not based on defined rules.

The theoretical dose of carboplatin was defined as the dose that would have been derived from the Calvert formula, in which eGFR is calculated by CG using actual Scr.

Statistics. The difference in eGFR based on demographics (gender and age) was analyzed using the Mann-Whitney non-parametric test. Changes in Scr and GFR at different time points based on BMI, PS, stage, histology and chemotherapy medication were analyzed using one-way ANOVA (Bonferroni) post-hoc multiple comparisons. Repeated measures analysis was used to compare the test results of eGFR in the first three chemotherapy cycles for all patients and for different groups segmented by the various parameters (BMI, PS, stage, histology and chemotherapy medication). The data were processed using SPSS for Windows (version 18), and a P-value <0.05 was considered to indicate a statistically significant result.

Table I. Characteristics of 117 NSCLC patients treated with carboplatin-based chemotherapy.

Characteristic	Value
Patients (M/F)	99/18
Median age (range)	62 (41-86) years
Median baseline creatinine (M/F)	0.85 (0.88/0.73) mg/dl
Range	0.40-1.3 mg/dl
Median GFR (Cockroft and Gault) (M/F)	81.3 (81.3/82.5) ml/min /1.73m^2
Range	31-168 ml/min/1.73m^2
GFR, n (%)	
30-59 ml/min/1.73m^2	19 (16)
60-89 ml/min/1.73m^2	55 (47)
90-119 ml/min/1.73m^2	26 (22)
>120 ml/min/1.73m^2	17 (15)
Performance status (ECOG), n (%)	
0	15 (13)
1	74 (63)
2	27 (23)
Unknown	1 (0.9)
Body mass index (BMI), n (%)	
Underweight (BMI <18.5)	4 (3.5)
Normal range (18.5≥BMI≤24.9)	50 (42.5)
Overweight (25≥BMI≤29.9)	49 (42)
Obese (BMI ≥30)	14 (12)
Histology, n (%)	
Squamous cell carcinoma	31 (26.5)
Adenocarcinoma	51 (43.5)
NSCLC non-specified	35 (30)
Drug used in combination with carboplatin, n (%)	
Gemcitabine	41 (35)
Paclitaxel	60 (51)
Pemetrexed	16 (14)
Stage (AJCC), n (%)	
IIIA/IIIB	66 (56.5)
IV	51 (43.5)

Results

Patient characteristics and renal function. The files of 126 consecutive patients with advanced NSCLC who had been treated with carboplatin-based combinations between January 2007 and June 2010 were reviewed. Nine patients were excluded from the study due to baseline creatinine levels >1.3 mg/dl. The main characteristics of the remaining 117 patients are presented in Table I. Most (85%) of the patients were male, and most (76%) of these had good PS; i.e., grade 0-1. Only four patients (3.5%) were underweight.

Table II. Fluctuations in theoretical carboplatin doses derived from Calvert formula[a].

Number of cycles	Number of patients	Increase of 20-50%	Increase 10-20%	No change ±10%	Reduction 10-20%	Reduction 20-40%
2	113	14 (12.4%)	10 (8.8%)	69 (61.1%)	14 (12.4%)	6 (5.3%)
3	94	12 (12.8%)	9 (9.6%)	62 (66%)	8 (8.5%)	3 (3.2%)
4	73	9 (12.3%)	15 (20.5%)	36 (49.3%)	8 (11%)	5 (6.8%)
5	40	0	10 (25%)	21 (52.5%)	4 (10%)	5 (12.5%)

[a]Using recent serum creatinine level at the beginning of each cycle for GFR estimation compared with baseline level.

Table III. Difference between actual prescribed carboplatin doses and theoretical carboplatin doses[a].

Number of cycles	Number of given cycles	Prescribed dose higher than theoretical by ≥10%	Difference of <10% between prescribed dose and dose derived from actual Scr	Prescribed dose lower than dose derived from actual Scr by ≥10%
1	117	12 (9%)	73 (63%)	32 (28%)
2-5	320	35 (11%)	176 (55%)	109 (34%)
Total	437	47 (10.8%)	249 (56.9%)	141 (32.3%)

[a]If calculated according to Calvert formula using Cockcroft and Gault estimated GFR and actual serum creatinine (Scr) level.

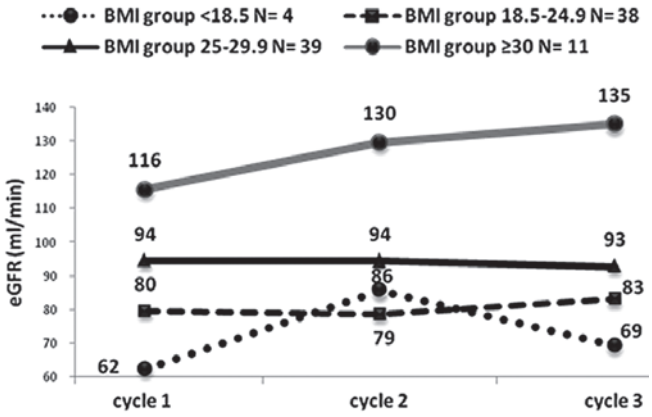

Figure 1. Changes in estimated creatinine clearance according to body mass index (BMI) during carboplatin-based chemotherapy treatment.

The median baseline creatinine level was 0.8 mg/dl for 45 males aged <60 years and 0.92 mg/dl for 61 males aged ≥60 years. The median level was 0.85 mg/dl for six females aged <60 years and 0.73 mg/dl for 14 females aged >60 years.

The median baseline GFR calculated according to Cockcroft and Gault was 82 ml/min, with no significant gender difference (P=0.9). The GFR was significantly higher in patients <60 years than in older patients (97 versus 72 ml/min; P=0.001). There was no significant gender difference in the average eGFR values. Since poor PS and weight loss may be associated with muscle waste, the correlation between those parameters and GFR (adjusted to ml/min/1.73 m^2) was tested. No significant difference was noted between PS 0-1 and PS 2. The number of patients with BMI <18.5 was too small to allow for statistical analysis.

Fluctuations in the full theoretical carboplatin doses. The number of chemotherapy cycles ranged between two and seven (median, 4). The main reason for treatment discontinuation was tumor progression. Changes in the full theoretical doses of carboplatin that would have resulted from prescribing 100% of the dose and using recent Scr levels for dose calculation are shown in Table II. Since a change of >10% was considered clinically significant, the results are expressed as changes of 10-20% and >20%. A total of 320 chemotherapy cycles were administered between cycles 2-5 for the entire study population. If treatment had been administered according to the CG formula only, 79/320 of the cycles (24.7%) would have been administered in doses >10% higher, and 53/320 (16.6%) in doses >10% lower than the theoretical baseline dose of carboplatin. This difference between the rate of dose increase of >10% and dose decrease of >10% was statistically significant (P=0.015) and correlated with changes in creatinine levels during the course of treatment. Compared with the baseline level, Scr increased by >10% in 69/320 (21.5%) cycles and decreased by >10% in 69/320 (28.7%) cycles.

Effect of various pretreatment parameters on fluctuations in eGFR. The trend for change in CG eGFR over the course of chemotherapy was assessed in 94 patients who completed at least three cycles of treatment. Fluctuations in eGFR during the treatment period were evaluated in correlation with the following parameters: BMI, PS, chemotherapy regimen, stage and histology.

BMI is the only parameter to predict changes in eGFR at a significant level of confidence. Patients with BMI ≥30 had a significant tendency for increased eGFR during subsequent chemotherapy treatments, with P=0.02, P=0.001 and P=0.01

for BMI <18.5, 18.5≥BMI≤24.9 and 25≥BMI≤29.9, respectively, and P=0.009 for all groups combined (Fig. 1). The trend for fluctuations in GFR did not differ significantly between patients with PS grade 2 and PS grade 0-1.

Physicians' decisions on carboplatin doses. The impact of using a modified Scr according to the physicians' discretion was evaluated by comparing actual prescribed doses to theoretical doses derived from the Calvert formula, which would have resulted had the recent Scr levels been used in the CG eGFR calculation. Differences of ≥10% were considered clinically significant. As shown in Table III, the prescribed dose was changed by >10% in 43.1% of the doses due to Scr modification. Clinicians tended to decrease the given dose rather than increase it. In approximately one-third of the chemotherapy cycles, the oncologist preferred to artificially input a higher Scr value into the computerized system than that actually measured, resulting in a dose decrease of >10%.

Discussion

Carboplatin dosing according to the Calvert formula is based on the assumption that the main mechanism of clearance of this drug is glomerular filtration. Although creatinine clearance consists of both glomerular filtration and tubular secretion, the use of creatinine clearance as a surrogate for GFR for drug dose calculation is generally accepted. GFR measurement based on radiolabeled isotopes is accurate but expensive, and a 24-h urine collection is inaccurate and cumbersome. Therefore, several mathematical equations have been developed to estimate GFR based on the assumption that serum creatinine is a marker for estimating GFR. Of these equations, CG is widely used in the clinical setting, including for the estimation of GFR in the Calvert formula. Although widely used in daily practice, CG, as well as other formulas for GFR estimation, has significant limitations in cancer patients (6). Recently, the new Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula was found to have failed as an estimate of GFR in cancer patients and as a clinical alternative to isotope tests (7). The current study was specifically aimed at evaluating the reliability of CG for carboplatin dose calculation according to the Calvert formula in patients with advanced NSCLC.

CG assumes that muscle mass is proportional to body weight. However, since creatinine production is influenced by several factors, including muscle mass, physical condition and nutrition, this equation may not accurately reflect the actual cortical collecting tubule. Muscle waste in these patients could result in an overestimation of GFR and, therefore, in an overdose of carboplatin when relying on the Calvert formula using CG and actual Scr for GFR calculation. To test this hypothesis we retrospectively analyzed the Calvert formula-calculated carboplatin doses, based on actual Scr and CG eGFR in patients with advanced NSCLC.

Due to the current study design it is impossible to determine whether the baseline CG eGFR was indeed overestimated. However, the median GFR of 81.3 ml/min/1.73 m^2 prior to the onset of chemotherapy was not obviously lower than that expected for a similar non-cancer population, as was found in the JUPITER study (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin). This trial included 16,279 participants, with a median GFR of 73.6 ml/min/1.73 m^2 calculated using the MDRD equation (8). The apparent lack of underestimation of baseline eGFR could be explained by the fact that only 3.5% of the patients were underweight and the majority (77%) had a good PS.

The range of eGFR among cancer patients at the beginning of chemotherapy treatment was evaluated in the retrospective analysis of the renal insufficiency and anticancer medications (IRMA) study (9). In a subgroup analysis of 445 patients with lung carcinoma from the IRMA study, the rate of GFR <60 ml/min was 23.5% and the rate of GFR >90 ml/min was 31.5% (10). A similar distribution of baseline GFR was found in the current study, with 16% with eGFR <60 ml/min and 37% with eGFR >90 ml/min.

In the current study, CG eGFR varied widely during the course of chemotherapy, resulting in clinically significant changes (i.e., >10%) in the theoretical Calvert formula-derived carboplatin dose in 41% of subsequent cycles. Furthermore, the dose of carboplatin derived from the Calvert formula and CG eGFR was increased by >10% in approximately a quarter of subsequent cycles, while it was decreased by >10% in only 17% of cycles (P=0.015).

No apparent association was found between the baseline CG eGFR and the tendency for fluctuations in eGFR in subsequent cycles. Notably, the tendency for increases in CG eGFR was most pronounced in obese patients (BMI >30) due to more significant decreases in Scr levels during the course of chemotherapy in these patients.

Carboplatin is an important drug in the treatment of ovarian carcinoma patients. The correlation between BMI and carboplatin dosing and treatment outcome was tested in several studies. Recently, in the Scottish Randomized Trial in Ovarian Cancer (SCOTROC) study, more than 1,000 patients were recruited and no association was found between BMI and survival or BMI and carboplatin dose intensity (11). In the SCOTROC study, one of the inclusion criteria was GFR measurement by plasma clearance of EDTA or 24-h urine collection for creatinine clearance. This demand was based on the conclusion of certain studies that eGFR is not reliable in obese patients (12). In our study, 12% of patients had severe obesity and high eGFR prior to and during chemotherapy treatment. A call for greater caution in estimating GFR in these patients, and possibly a recommendation for urine collection for creatinine clearance, is reasonable.

During the study period there were no firm guidelines at our institution on how to compensate for fluctuations in Scr levels in the actual computerized prescription of carboplatin. In approximately one-third of chemotherapy cycles, we found that there was a reduction of more than 10% in the actual carboplatin doses prescribed by the physician compared with the doses calculated according to the Calvert formula. Whether or not the physician's preference was to artificially lower the prescribed carboplatin dose is unknown.

In conclusion, Calvert formula-derived carboplatin doses fluctuate widely during repeated cycles in patients with advanced NSCLC where actual Scr is used for CG GFR estimation. Discrepancies of >10% compared with the initial dose were found in more than 40% of subsequent doses. Approximately a quarter of theoretical subsequent doses were

more than 10% higher than the initial dose due to decreases in Scr.

Physicians tend to prescribe a lower dose than that derived from the Calvert formula by using a higher Scr than that actually measured. Thus, reconsidering the measurement of 24-h creatinine clearance as a feasible alternative in selected patients with observed Scr reduction during therapy is recommended.

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