

Impact of rounding low serum creatinine concentrations on the accuracy of carboplatin AUC dosing

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ABSTRACT

Study objectives: Calculating carboplatin dosing using the Calvert, and Cockcroft and Gault formulae, in patients with low serum creatinine levels, has been the subject of controversial discussion. A retrospective analysis was conducted to find out whether or not rounding of low serum creatinine concentrations improves accuracy of the carboplatin dose.

Methods: Data were collected retrospectively from 128 adult lung cancer patients with serum creatinine < 0.8 mg/dL (71 µmol/L) who had received chemotherapy that was mostly platinum-based. The measured creatinine clearance (24-hour urine collection) and estimated creatinine clearance, according to the Cockcroft and Gault formula, were available on the same day from these patients. Carboplatin doses were recalculated using measured creatinine clearance and estimated creatinine clearance with a rounded serum creatinine value of 0.8 mg/dL and compared with the administered dose calculated with actual serum creatinine using the Cockcroft and Gault formula. Subgroup analyses were performed for serum creatinine < 0.6 mg/dL, gender and body mass index (BMI).

The same procedure was performed for a subgroup of 56 patients with serum creatinine < 0.68 mg/dL (60 µmol/L) setting the cut-off level at 0.68 mg/dL with the following subgroup analyses: gender, BMI, creatinine clearance (24-hour urine collection) and creatinine clearance (Cockcroft-Gault).

Results: Bias of the mean carboplatin dose worsened from 4% to -11% in the whole patient population by rounding serum creatinine to 0.8 mg/dL but improved mainly for patients with BMI ≥ 25. Rounding to 0.68 mg/dL in the respective subgroup improved bias from 10% to -4% with the greatest benefit for overweight and obese patients, but increasing the potential of underdosing from -3% to -15% especially for normal weight and cachectic patients. When rounded to 0.68 mg/dL, bias also worsened for male patients from -5% to -16% and from -14% to -20% for patients with creatinine clearance (Cockcroft-Gault) ≤ 100 mL/minute.

Conclusion: The results show that rounding low serum creatinine values to 0.8 mg/dL bore the risk of underdosing the patient population with carboplatin. Rounding to 0.68 mg/dL seemed to be more favourable, especially in overweight and obese patients but with the potential of underdosing regarding normal weight and cachectic patients.

KEYWORDS

Carboplatin, Cockcroft and Gault, cytotoxic agent, renal function, serum creatinine

INTRODUCTION

Tailoring doses of cytotoxic drugs to individual cancer patients is common practice today; however, there are unsolved questions regarding dosing with such drugs. For

example, the dosing of many cytotoxics according to the patient's body surface area is frequently questioned [1]. For carboplatin, which is renally excreted, a very close relationship between its dose, area under the concentration time curve (AUC), toxicity and therapeutic effect can be demonstrated and allow it to be suitable for individualised dosing based on renal function and the Calvert formula [2]: dose = target AUC [mg/mL x min] x (glomerular filtration rate (GFR) [mL/min] + 25) [3, 4]. Because the ⁵¹chromium-labelled ethylenediaminetetraacetate (⁵¹CrEDTA) method used by Calvert is too costly and time-consuming for routine measurement of GFR, most clinicians use the Cockcroft and Gault (C-G) formula for estimating renal function [5]:

Creatinine clearance (CrCl) [mL/min] = (140 - age) x weight [kg] x 0.85 (if female)/(72 x serum creatinine (SCr) [mg/dL]).

With the introduction of the C-G and other formulae, a discussion started about systematic dosing inaccuracies

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Received: 28 September 2010, Revised manuscript received: 1 March 2011; Accepted 2 March 2011

caused by suboptimal estimation of renal function compared with the original $^{51}\text{CrEDTA}$ method [3]. For example, Poole et al. examined different formulae for GFR calculation in 122 cancer patients and found that the C-G formula using actual body weight overestimated renal function in patients with $\text{GFR} < 50$ mL/minute and underestimated renal excretion in patients with $\text{GFR} > 100$ mL/minute in both sexes [6, 7] compared with the technetium $^{99\text{m}}$ diethylene triamine pentaacetate ($\text{Tc}^{99\text{m}}$ DTPA) method for clearance measurement which is comparable with the $^{51}\text{CrEDTA}$ method as a gold standard.

There has also been considerable focus on the use of CrCl as a marker for GFR. Renal clearance of creatinine is not only because of glomerular filtration but also by tubular secretion and leads, therefore, to an overestimation of GFR between 12% and 24%. If the colorimetric alkaline picrate method (Jaffé method) is used for creatinine detection this can result in an overestimation of SCr of 20–30% because of interfering substances (non-creatinine chromogens) in serum samples but not in urine; this method can therefore result in an underestimation of GFR. By coincidence, this error approximately compensates the difference between true CrCl and GFR. Hence, a correction of the calculated dose of carboplatin may not be necessary in this setting [8]. If an enzymatic assay is used for SCr measurement, this can result in an overestimation of GFR and the resulting carboplatin dose. Léger et al. demonstrated that using the Chatelut formula to estimate carboplatin clearance resulted in a difference of 13.9% between an enzymatic SCr assay and the kinetic method [9]. A difference of about 10% between these two methods was also found by Levey et al. regarding the modification of diet in renal disease equation [10]. This possible systematic error also affects the C-G formula but is not always considered for renal clearance calculation in clinical practice.

With regard to overweight patients in particular, much attention has been paid to the kind of weight descriptor used for dose calculation. Among others, lean body mass (also lean body weight, LBW) according to Janmahasatian et al. has been studied in adult oncology patients, general medical patients and healthy volunteers [11, 12]. While some suggest using LBW for calculating drug dosage [13] others found no or only slightly clinically significant improvements in dose calculation for some cytotoxic drugs including carboplatin when LBW instead of actual body weight was used to calculate drug dose in obese oncology patients [14]. Referring to carboplatin, Mathijssen et al. comment on these findings: 'Even though encouraging results were obtained for carboplatin . . . the clinical utility of this finding may be negligible, because dose calculations

for this agent are typically based on measures of renal function, not body size' [15]. Another weight descriptor, adjusted body weight, led to a more accurate carboplatin dose calculation for overweight and obese cancer patients than the use of total body weight in the C-G formula [16, 22] and deserves further examination.

The possible inaccuracies of calculating renal clearance in patients with low SCr concentrations have been examined in several studies. Bertino examined 33 patients with stable renal function and $\text{SCr} < 0.96$ mg/dL (85 $\mu\text{mol/L}$) receiving total parenteral nutrition and found that actual SCr value should be used in the C-G formula instead of rounding to $\text{SCr} = 0.96$ mg/dL [17]. For accurate aminoglycoside dosing in 23 elderly patients with $\text{SCr} < 1.0$ mg/dL, Smythe et al. compared renal function estimates via C-G with either actual SCr or rounded $\text{SCr} = 1.0$ mg/dL and found that rounding led to strong underestimation of renal function (bias -22.6%) whereas calculation with actual SCr led to non-significant modest overdosing of 5.2% [18]. In contrast, Duffull et al. found in 12 female cancer patients receiving carboplatin (not mentioning the number of patients with $\text{SCr} < 0.68$ mg/dL) that the C-G equation using the lower of LBW or total body weight (dosing weight) and adjusting SCr to 0.68 mg/dL (60 $\mu\text{mol/L}$) provided a better description of carboplatin clearance than $\text{Tc}^{99\text{m}}$ DTPA clearance [19]. The same authors examined 957 patients receiving gentamicin, of whom 208 had SCr levels lower than 0.68 mg/dL; they concluded that rounding low values of SCr to 0.68 mg/dL before using C-G (with dosing weight instead of total body weight, see above) gave a better estimate of the patient's gentamicin clearance. The authors indicated that rounding will not detect a change of SCr values beneath this threshold and thus ignore potential declining of renal function [20].

A new attempt to overcome the limitations of existing methods for estimating CrCl that rely only on the serum marker creatinine (together with demographical and morphological factors) like the C-G formula, uses cystatin C (cysC) as an additional biological covariate. CysC is a small protein that is produced endogenously at a constant rate and is not renally secreted; it is therefore supposed to meet the criteria for an ideal GFR marker. Regarding dose calculation of carboplatin, a new formula containing cysC and creatinine as serum markers led to encouraging results in different patient populations including patients with low SCr values. However, cysC determination is not available in many clinical laboratories at present [21].

The present work focuses on possible dosing inaccuracies in cancer patients with low serum creatinine values of less

than 0.8 mg/dL (71 µmol/L) and addresses the current practice in the Heidelberg Clinic for Thoracic Diseases of rounding values ≤ 0.6 mg/dL (53 µmol/L) up to 0.8 mg/dL, which was adopted in May 2006 according to the work of Herrington et al. [22] with the obligation to prove this practice in an investigation at the clinic. Furthermore, it was investigated whether or not rounding low serum creatinine values can result in a more accurate dose calculation solely for patients with GFR (C-G) ≤ 100 mL/minute as proposed by Dooley et al. for a cut-off value of 0.68 mg/dL (60 µmol/L) serum creatinine [23]. The results of Herrington et al. and Dooley et al. are described in the discussion section in more detail.

METHOD

Data from 128 adult lung cancer patients were obtained retrospectively from local records in the clinic, especially the pharmacy department (for patient data, see Table 1). Criteria for inclusion were:

- patients presented with SCr < 0.8 mg/dL
- patients were receiving chemotherapy, mostly platinum-based, in the years 2005–2007
- values for SCr and CrCl calculated from 24-hour urine collection were available on the same day.

Most patients received carboplatin with a target AUC of 5, calculated according to the Calvert and C-G formulae, using actual SCr values. For the remaining patients receiving another chemotherapeutic regimen instead of carboplatin, the dose was calculated with actual SCr as if these patients had received carboplatin. These resulting doses were compared with the corresponding recalculated doses using either the Calvert formula with CrCl derived from 24-hour urine collection or Calvert and C-G formulae

with a rounded SCr value of 0.8 mg/dL (71 µmol/L) for the whole patient population and different subgroups (SCr ≤ 0.6 mg/dL as mentioned in the introduction section: gender, BMI according to the WHO classification for underweight/normal weight (< 25), overweight (≤ 25) and obese (≥ 30) respectively [24], using bias and precision.

The same procedure was performed for a subgroup of 56 patients with SCr < 0.68 mg/dL (60 µmol/L) setting the cut-off value at 0.68 mg/dL. Here, subgroup analyses were performed according to gender, BMI, CrCl (C-G) ≤ 100 mL/minute, CrCl (C-G) > 100 mL/minute and CrCl (24-hour urine collection) ≤ 100 mL/minute and CrCl (24-hour urine collection) > 100 mL/minute.

Bias was assessed as mean percentage error (MPE), calculated as the percentage difference between estimated and measured CrCl. A positive bias indicated overestimation of CrCl and a negative bias indicated underestimation. Precision was calculated as mean absolute percentage error (MAPE). The larger the MAPE, the less precise the calculation results in predicting actual CrCl and hence GFR.

$$\text{MPE} [\%] = 1/n \times \sum (D - D_{\text{CrCl}}) \times 100/D_{\text{CrCl}}$$

$$\text{MAPE} [\%] = 1/n \times \sum |D - D_{\text{CrCl}}| \times 100/D_{\text{CrCl}}$$

*24 h urine collection

D refers to the carboplatin dose either calculated with actual SCr or rounded SCr (0.8 mg/dL or 0.68 mg/dL respectively) and $D_{\text{CrCl (24 h urine collection)}}$ refers to the carboplatin dose calculated with CrCl from 24-hour urine collection.

Total body weight was always used in the C-G formula for estimating renal function. For the CrCl reference method

Table 1: Patient characteristics

	Mean all (range) n = 128	Mean males (range) n = 56	Mean females (range) n = 72	Mean SCr < 0.68 mg/dL (range) n = 56
Age (years)	59 (35–80)	60 (40–80)	58 (35–78)	57 (38–78)
Height (cm)	168 (151–196)	174 (160–196)	164 (151–177)	167 (151–182)
Weight (kg)	69.4 (34.0–114.0)	76.7 (49.0–114.0)	63.7 (34.0–92.0)	66.6 (34.0–102.0)
BMI (kg/m ²)	24.4 (13.6–40.4)	25.2 (17.8–40.4)	23.8 (13.6–34.3)	24.0 (13.6–37.5)
BSA (Mosteller) (m ²)	1.79 (1.22–2.37)	1.92 (1.48–2.37)	1.69 (1.22–2.08)	1.75 (1.22–2.25)
Serum creatinine (mg/dL)	0.67 (0.38–0.79)	0.69 (0.40–0.79)	0.65 (0.38–0.78)	0.58 (0.38–0.67)
Creatinine clearance (24 h urine collection) (mL/min)	113 (21–269)	136 (55–269)	96 (21–171)	119 (21–269)
Creatinine clearance (C-G) (mL/min)	109 (60–232)	124 (65–186)	97 (60–232)	119 (61–232)

SCr: serum creatinine; BMI: body mass index; BSA: body surface area; C-G: Cockcroft and Gault

(24-hour urine collection), the nursing staff instructed patients to collect their urine for 24 hours, beginning in the morning, and to drink a sufficiency during this time. If the collected urine volume was implausibly low, this sample was discarded. From the resulting urine volume per 24 hours (V_{24}) and the creatinine concentrations in urine (UCr) and serum (SCr), CrCl (24-hour urine collection) was calculated as follows:

CrCl (24-hour urine collection)[mL/minute] = V_{24} [mL] x UCr[mg/dL] x 1,440 / SCr[mg/dL]; 1,440: converting factor from 24 hours to one minute.

Serum creatinine was measured using a kinetic Jaffé method [HiCo Creatinine Jaffé method, rate-blanked, with compensation, traceable to isotope dilution mass spectrometry (IDMS), Roche Diagnostics] until June 2006, and an enzymatic method thereafter [Konelab/T Series creatinine (Enzymatic), IDMS traceable, Thermo Fisher Scientific].

Furthermore, the non-parametric Wilcoxon matched-pairs test with a level of significance of $p = 0.05$ was used to compare results from measured and estimated CrCl. A non-parametric Spearman's rank test was applied to examine the correlation between measured CrCl (24-hour urine collection) and estimated CrCl (C-G). Calculations were done with Microsoft Excel Office XP and SPSS version 17.0.

RESULTS

Rounding low serum creatinine concentrations to 0.8 mg/dL (71 μ mol/L)

Rounding low serum creatinine levels to 0.8 mg/dL (71 μ mol/L) significantly worsened the bias of mean carboplatin doses in the overall population of 128 adult lung cancer patients compared with the use of actual SCr values relating to measurement of CrCl by 24-hour urine collection from 4% unrounded to -11% rounded. There was no gender-specific difference in this trend for the 56 males and 72 females. Bias for the 27 patients with SCr < 0.6 mg/dL was more precise when rounded to 0.8 mg/dL but a mean underdosing of 16% occurred compared with a mean of 20% overdosing without rounding. Bias was also improved for the 47 overweight and obese patients with BMI ≥ 25 (bias rounded 5–8% versus bias unrounded 24–25%). For the subgroup of 81 underweight and normal-weight patients, rounding low SCr values increased the risk of underdosing from a mean bias of 8% to 21%. Rounding SCr values < 0.6 mg/dL to 0.8 mg/dL ($n = 27$) improved bias from 20% to -16% with no significant change in precision, see Table 2.

Rounding low serum creatinine concentrations to 0.68 mg/dL (60 μ mol/L)

In the subpopulation of 56 lung cancer patients with SCr < 0.68 mg/dL (60 μ mol/L) rounding SCr values to

Table 2: Carboplatin AUC 5 doses resulting from measured (24-hour urine collection) and estimated (C-G with actual and rounded SCr values) CrCl with according bias (as MPE), precision (as MAPE) and significance p (Wilcoxon) for patients with SCr < 0.8 mg/dL

	Mean dose \pm SD according to Calvert/CrCl (24-hour urine collection) (mg)	Mean dose \pm SD according to Calvert/C-G with actual SCr (mg)	Mean dose \pm SD according to Calvert/C-G with rounded SCr = 0.8 mg/dL (mg)	MPE Calvert/C-G with actual SCr (%)	MPE Calvert/C-G with rounded SCr = 0.8 mg/dL (%)	p MPE	MAPE Calvert/C-G with actual SCr (%)	MAPE Calvert/C-G with rounded SCr = 0.8 mg/dL (%)	p MAPE
All, $n = 128$	691 \pm 208	670 \pm 157	574 \pm 115	4	-11	< 0.002	25	25	0.11
Males, $n = 56$	804 \pm 222	747 \pm 140	655 \pm 101	-1	-12	< 0.002	23	26	0.06
Females, $n = 72$	604 \pm 147	611 \pm 144	511 \pm 117	8	-10	< 0.002	27	24	0.62
SCr < 0.6 mg/dL $n = 27$	709 \pm 225	800 \pm 171	638 \pm 111	20	-16	< 0.002	33	26	0.35
BMI < 25 kg/m ² $n = 81$	705 \pm 196	618 \pm 120	530 \pm 92	-8	-21	< 0.002	20	24	< 0.001
25 \leq BMI < 30 kg/m ² $n = 32$	647 \pm 235	725 \pm 171	627 \pm 105	24	8	< 0.002	36	27	0.06
BMI \geq 30 kg/m ² $n = 15$	716 \pm 211	835 \pm 155	699 \pm 119	25	5	< 0.002	33	25	0.11

AUC: area under the concentration time curve; C-G: Cockcroft and Gault; SCr: serum creatinine; CrCl: creatinine clearance; MPE: mean percentage error; MAPE: mean absolute percentage error; SD: standard deviation; BMI: body mass index.

0.68 mg/dL improved bias significantly from 10% to -4%. The subgroup of 38 female patients benefited from rounding whereas the male subgroup (18 patients) did not. Twenty-two patients with a measured CrCl \leq 100 mL/minute benefited on average from rounding low SCr levels to 0.68 mg/dL (bias 27% compared with 46% using actual SCr) whereas the 34 patients with measured CrCl $>$ 100 mL/minute did not (bias -24% rounded versus -13% unrounded). On the contrary, if patients were grouped according to their estimated CrCl using C-G and a cut-off value of CrCl = 100 mL/minute (calculated with actual SCr), bias in 19 patients with CrCl \leq 100 mL/minute worsened from -14% to -20% when rounded SCr values were used, whereas bias improved from 22% with actual SCr to 5% when rounded to 0.68 mg/dL in 37 patients with CrCl (C-G) $>$ 100 mL/minute. Bias also improved on average in 10 patients with a BMI of about 25 but under 30 (55% unrounded versus 31% rounded) and in eight patients with BMI \geq 30 (17% unrounded versus 5% rounded), see Table 3.

In general, for all patients with SCr $<$ 0.8 mg/dL, precision lay between 23% and 36% across the studied subgroups and between 19% and 64% for patients with SCr $<$ 0.68 mg/dL.

Spearman's rank correlation test gave a moderate positive correlation of $p = 0.34$ between measured CrCl (24-hour urine collection) and estimated CrCl (C-G) for the 128 patients with SCr $<$ 0.8 mg/dL and a correlation $p = 0.22$ for the 56 patients with SCr $<$ 0.68 mg/dL.

DISCUSSION

Rounding low serum creatinine concentrations to 0.8 mg/dL (71 μ mol/L)

Rounding low serum creatinine levels to 0.8 mg/dL (71 μ mol/L) in 128 adult patients with lung cancer worsened bias and could not improve precision of carboplatin dosing compared with the use of actual SCr values when measurement of CrCl by 24-hour urine collection was used as standard. A significant improvement of dosing

Table 3: Carboplatin AUC 5 doses resulting from measured (24-hour urine collection) and estimated (C-G with actual and rounded SCr values) CrCl with according bias (as MPE), precision (as MAPE) and significance p (Wilcoxon) for patients with SCr $<$ 0.68 mg/dL

	Mean dose \pm SD according to Calvert/CrCl (24-hour urine collection) (mg)	Mean dose \pm SD according to Calvert/C-G with actual SCr (mg)	Mean dose \pm SD according to Calvert/C-G with rounded SCr = 0.68 mg/dL (mg)	MPE Calvert/C-G with actual SCr (%)	MPE Calvert/C-G with rounded SCr = 0.68 mg/dL (%)	p MPE	MAPE Calvert/C-G with actual SCr (%)	MAPE Calvert/C-G with rounded SCr = 0.68 mg/dL (%)	p MAPE
All, n = 56	719 \pm 232	722 \pm 169	630 \pm 130	10	-4	$<$ 0.002	31	27	0.57
Males, n = 18	921 \pm 242	825 \pm 145	731 \pm 119	-5	-16	$<$ 0.002	20	25	$<$ 0.01
Females, n = 38	623 \pm 153	674 \pm 160	582 \pm 107	17	2	$<$ 0.002	35	29	0.51
BMI $<$ 25 kg/m ² , n = 38	724 \pm 218	657 \pm 128	575 \pm 100	-3	-15	$<$ 0.005	23	24	$<$ 0.05
25 \leq BMI $<$ 30 kg/m ² , n = 10	638 \pm 279	845 \pm 198	704 \pm 93	55	31	$<$ 0.005	64	46	$<$ 0.05
BMI \geq 30 kg/m ² , n = 8	796 \pm 234	883 \pm 118	798 \pm 113	17	5	$<$ 0.02	25	19	0.31
CrCl (C-G) \leq 100 mL/min, n = 19	667 \pm 145	550 \pm 54	508 \pm 62	-14	-20	$<$ 0.002	20	22	$<$ 0.05
CrCl (C-G) $>$ 100 mL/min, n = 37	745 \pm 263	811 \pm 136	692 \pm 110	22	5	$<$ 0.002	36	30	0.30
CrCl (24-hour urine collection) \leq 100 mL/min, n = 22	512 \pm 85	720 \pm 184	623 \pm 112	46	27	$<$ 0.002	48	31	$<$ 0.001
CrCl (24-hour urine collection) $>$ 100 mL/min, n = 34	852 \pm 195	724 \pm 162	635 \pm 142	-13	-24	$<$ 0.002	19	25	$<$ 0.002

AUC: area under the concentration time curve; C-G: Cockcroft and Gault; SCr: serum creatinine; CrCl: creatinine clearance; MPE: mean percentage error; MAPE: mean absolute percentage error; SD: standard deviation; BMI: body mass index

accuracy via rounding SCr to 0.8 mg/dL could be shown for 47 patients with BMI \geq 25.

The practice in this clinic of rounding low SCr values of \leq 0.6 mg/dL (53 μ mol/L) to 0.8 mg/dL was adopted according to the findings of Herrington et al. [22] with the obligation to prove this decision in an investigation which was performed in the present study. The work of Herrington et al. addressed rounding SCr levels lower than 0.8 mg/dL to 0.8 mg/dL (71 μ mol/L) in five male and four female cancer patients with BMI between 18.6 and 25.3, and SCr values 0.40–0.70 mg/dL, who were receiving carboplatin-containing chemotherapy. The study by Herrington et al. used the C-G equation with actual body weight for GFR estimation. Calculating renal clearance with actual SCr resulted in a high overdose (measured carboplatin AUC 7.8 instead of target AUC 5.1). Rounding to 0.8 mg/dL could have resulted in an AUC of 5.6. These findings are in contrast to those at the Heidelberg Clinic for Thoracic Diseases where rounding to SCr = 0.8 mg/dL worsened bias from -8% to -21% in 81 patients with BMI between 13.6 and 25. Based on these results, it seems questionable whether rounding low SCr levels to 0.8 mg/dL is generally adequate. For patients with BMI \geq 25 there was an improved dosing accuracy so that rounding low SCr values in this population is probably beneficial. The current practice in the Heidelberg clinic—rounding SCr values $<$ 0.6 mg/dL to 0.8 mg/dL—changed the carboplatin dose from an average 20% overdose to a mean 16% underdose.

Rounding low serum creatinine concentrations to 0.68 mg/dL (60 μ mol/L)

Rounding low serum creatinine levels to 0.68 mg/dL (60 μ mol/L) in 56 adult lung cancer patients could improve bias of mean carboplatin dose in contrast to rounding to 0.8 mg/dL (71 μ mol/L). Improvement was found in the female participants of the study whereas the male subgroup did not benefit from rounding.

The method used by Dooley et al. [23] to calculate the cut-off level is somewhat cumbersome, as described below. For this reason, the method of Dooley et al. was not adopted in the Heidelberg clinic. Instead, the work of Herrington et al. was followed for dosing guidance in patients with low SCr levels who were receiving carboplatin [22]. Dooley et al. looked at rounding low SCr values in 15 female and 11 male cancer patients with SCr $<$ 0.68 mg/dL (60 μ mol/L). The researchers found that rounding to 0.68 mg/dL before using SCr in the C-G formula with actual body weight led to an underestimation of renal function of 7% whereas actual values overestimated CrCl by 12.9%. If the patients had a

measured [Tc^{99m}] DTPA clearance of \leq 100 mL/minute, MPE improved from 29.2% to 7.9% by rounding, whereas for patients with [Tc^{99m}] DTPA clearance $>$ 100 mL/minute, rounding worsened the GFR estimation from -0.1% to -18.9%. The authors explained this difference with two possible reasons for low SCr concentrations: either low production or high clearance of creatinine. If patients have a low measured CrCl (\leq 100 mL/minute) and simultaneously a low SCr value, the reason for this low value is more likely to be low production of creatinine rather than high excretion. In this case, the authors recommended rounding to SCr = 0.68 mg/dL to avoid an overestimation of the actual clearance. On the other hand, if patients have a high CrCl ($>$ 100 mL/minute) the reason for a low SCr value is more likely to be high clearance of creatinine so that the authors did not see any reason for an arbitrary restriction of GFR to a value higher than the actual SCr.

Based on their own findings, Dooley et al. recommended calculating CrCl with C-G and actual SCr value first and then recalculating CrCl with SCr of 0.68 mg/dL if the result of the first calculation is \leq 100 mL/minute [23]. For this algorithm they assumed that C-G clearance correlates well with measured clearance, which is not necessarily the case. In the analysis of the present study, a weak correlation of $p = 0.22$ between measured CrCl (24-hour urine collection) and estimated CrCl (C-G) for the 56 patients with SCr $<$ 0.68 mg/dL was found; this is in concordance with the findings of others focusing on patients with low SCr values [25]. Rounding SCr to 0.68 mg/dL, in 22 cancer patients with measured CrCl (24-hour urine collection) \leq 100 mL/minute, reduced bias significantly.

On the contrary, rounding worsened GFR estimation in 19 patients with estimated CrCl (C-G) \leq 100 mL/minute, see Table 3. It is usual for only an estimated CrCl (C-G) to be known in clinical practice; therefore, based on the results at the Heidelberg clinic, rounding low SCr values, as Dooley et al. suggest, cannot be recommended generally for patients with CrCl (C-G) \leq 100 mL/minute. In contrast, when focusing on the patient's BMI, the fact that seven patients with BMI $>$ 25 in Dooley's study did benefit from rounding low SCr values is in concordance with the Heidelberg clinic data where rounding SCr to 0.68 mg/dL resulted in a significantly decreased bias in 18 patients with BMI \geq 25. In this respect, the Heidelberg clinic can follow their recommendation regarding this patient population. Looking at patients with BMI $<$ 25 it seems that the lower the patient's BMI in the study of Dooley et al. the lower the benefit of rounding low SCr values; there was a poorer outcome for four patients with BMI $<$ 18.5 compared with the result with actual SCr. The results in Heidelberg followed

the same trend because bias increased significantly for 38 patients with BMI < 25 [23].

Assumptions on the clinical significance of the results can be based on the generally accepted finding that the therapeutic window for carboplatin comprises AUC 5–7 [4]. Dosing regimens that lead to AUC 4 or below (or in other words a bias of -20% related to a target AUC 5) can therefore be regarded as subtherapeutic. Rounding low SCr values to 0.8 mg/dL or 0.68 mg/dL leads to a bias of less than -20% for most of the studied patient subgroups. Therefore the clinical implications of rounding low SCr levels could have been moderate for most of the patients. Nevertheless, managing a possible subtherapeutic dose could have been difficult in clinical practice because of not perceiving it as such. If, on the other hand, overdosing had occurred, clinicians were aware of it because of clinical signs such as haematological toxicities, and therefore were able to deal with it [26].

The study offers strengths and limitations. To begin with the strengths: to the researchers' knowledge, the study consisted of a far larger patient population than any previous study in cancer patients. This could lead to more reliable results and enables subgroup analyses with regard to SCr, gender, BMI and CrCl. Limitations of the study mainly result from the retrospective character and the possible uncertainties of measuring CrCl via 24-hour urine collection which is susceptible to error and is no longer routinely recommended to estimate the level of kidney function [27] but which is, nevertheless, the only available reference method for clinics with limited resources.

Besides, even suspected gold standard measurement procedures for determining kidney function like the iothalamate method have been found to be of questionable accuracy [28]. The fact that the patients at the Heidelberg Clinic for Thoracic Diseases did not necessarily receive carboplatin, but cisplatin or another chemotherapeutic regimen, did not alter the calculation of renal function and

thus the results. The use of two serum creatinine assays in the study period—a kinetic Jaffé method until June 2006 and an enzymatic method thereafter—did not affect the results substantially because all measurements for a certain patient were done with the same method. Possible CrCl values of higher percentage and hence carboplatin dosages resulting from lower SCr values assayed with the enzymatic method compared with the Jaffé method did not affect calculation of MPE (bias) and MAPE (precision).

CONCLUSION

Rounding low SCr values to 0.8 mg/dL in 128 adult lung cancer patients worsened bias and did not improve precision in estimating GFR with the C-G equation in the overall patient population. An improvement in dosing accuracy could be seen in overweight and obese patients. On the contrary, rounding low SCr levels to 0.68 mg/dL (60 µmol/L) improved carboplatin dosing accuracy in the subpopulation of 56 patients, especially in patients with BMI ≥ 25. Rounding low SCr levels to 0.68 mg/dL seems superior to rounding to 0.8 mg/dL even without the laborious calculation method proposed by Dooley et al. [23] and seems applicable especially to overweight and obese patients. Application to normal weight and cachectic patients requires caution; gender-specific differences should be examined further. Desirable future studies should be sufficiently powered and use a more reliable reference method for determining GFR than 24-hour urine collection. Only then can more definite conclusions for different patient groups be drawn and changes in clinical practice justified.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

The authors would like to thank Dr Thomas Muley for his biostatistical support and his valuable advice on the preparation of the manuscript and Ms Martina Schrenk for initial data extraction.

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