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ORIGINAL ARTICLE

Evaluation of a non cystatin-C-based novel algorithm to calculate individual glomerular filtration rate in cancer patients receiving carboplatin

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Abstract
Purpose The purpose of this study was to determine the potential utility of a novel algorithm to calculate individual GFR values in cancer patients. Based on carboplatin AUC measurements the algorithm-based values were compared with results related to other routinely used equations.
Methods The association between measured and predicted carboplatin AUC was examined by the Bland–Altman analysis to determine bias and precision. Based on the Calvert formula, GFR values assessed by different routes of calculation including the novel algorithm were compared with each other in individual patients.
Results The mean absolute administered carboplatin dose was 498 mg and the mean measured carboplatin AUC 5.8 mg/ml × min. Compared to the novel algorithm, the degree of bias to calculate carboplatin AUC was greater with the Cockcroft-Gault, Chatelut, Hoek and Schmitt formula which includes cystatin C as a parameter. In selected patients, algorithm-based GFR values were closer to GFR according to the Calvert formula than results of other equations, including the Jelliffe formula.
Conclusion These results suggest that the concept of a non cystatin C-based novel algorithm including three different formulas rather than one single equation may improve accurate estimation of GFR over a broad range of constitutive values, including patients with low constitutive renal function as well as overweight patients.

Keywords Novel algorithm · Carboplatin AUC · Glomerular filtration rate · Cystatin C

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Introduction

The anticancer drug carboplatin belongs to a well-defined group of agents which is highly excreted in unchanged form via glomerular filtration [1]. Based on its narrow therapeutic window and the well described correlation between AUC values and clinical efficacy as well as myelotoxicity [2–4], the Calvert formula (dose = target AUC × (GFR + 25)) has been established to improve the individualization of carboplatin-containing chemotherapy based on renal function instead of body surface area [5]. In this regard, accurate assessment of individual glomerular filtration rate (GFR) appears to be mandatory if theoretically calculated and clinically realized AUC values should be close to each other. However, in spite of multiple publications which have suggested that the probably best fitted formula might be available to calculate individual renal function, the results are still somewhat disappointing based on significant over- and underestimation of GFR [6–8].

Very recently, we proposed a novel algorithm to be beneficial compared to other available mathematical calculation strategies [9–11] because three formulas [11–13]

rather than one single formula may reflect the real situation of a broad GFR range more closely (Fig. 1) [14]. In order to prove the validity of this algorithm in clinical practice, we determined carboplatin-AUC values based on a limited sampling method by atomic absorption spectrometry (AAS) and compared the measured carboplatin AUC with predictive values calculated via different GFR ways substituted into the Calvert formula (Table 1). We include the broadly accepted Jelliffe- and Cockcroft-Gault formula [9, 10], the Hoek formula [15, 16] based on cystatin C measurements, as well as endogenous CrCl measurements based on 24-h urine collection and the novel algorithm [14]. In addition, in individual cases, for example overweight patients or renal insufficiency, we compared calculated GFR values with each other in regard to accuracy, over- and underestimation.

Methods

Enrollement of patients

We considered 40 patients and have to excluded 11. The reasons are: infusion duration longer than 1 h (>1 h ± 5 min), wrong urine collection, dead between written informt consent and starting therapy, carboplatin AUC 6 instead of AUC 5, adverse effect of carboplatin, interruption of chemotherapy and wrong or missed blood sampling time points. Therefore, the prospective analysis included 29 adult caucasian cancer patients with an underlying stable renal function who were scheduled to receive a carboplatin 1-h infusion with carboplatin AUC 5. Exclusion criteria were dialysis, anuria, renal tumor, bone marrow infiltration and hydration. All patients provided written informed consent. The study was performed after approval of the local institutional ethic committee review board of the Eberhard-Karls University of Tuebingen and was in accordance with the guidelines of the Declaration of Helsinki.

Pharmakokinetic assessment and calculation of carboplatin AUC

For the determination of carboplatin (free platinum) a limited sampling strategy published by Sorensen et al. was utilized [17]. Infusion duration and sampling time points were strictly controlled. Table 2 shows the actual duration of infusion of carboplatin and sampling time points of each patient. Blood samples (5 mL in EDTA collection tubes) were obtained before, at 0.25 h and 2.75 h after the beginning of the carboplatin 1-h infusion. All of the samples were centrifuged at 3,000 rpm for 10 min at 20°C within 15 min after collection. The ultrafiltrate plasma fraction representing the non-protein bound active carboplatin fraction, was prepared using the Amicon micropartition system with a YMT-14 membrane (30 kDa; Millipore Corp. Bredford, MA). A volume of 0.5 mL plasma was transferred in the micropartition system, centrifuged at 2,500 rpm for 20 min at 20°C and stored at –70°C until analyses. Analysis of platinum in ultrafiltrate were done using flameless atomic absorption spectrometry (SOLAAR MQZ Zeeman AAS, Thermo Optek), at Slotervaart Hospital, Amsterdam as described by van Warmerdam et al. [18]. The lower limit of quantitation (LLQ) of the assay was 0.5 μmol/L with the accuracy of less than ±14.6% and the within- and between-day precision less than ±7.9% and less than ±7.7%. A calibration curve platinum absorbance peak height versus carboplatin concentration in 10% ultrafiltrate was constructed and with a quadratic regression applied to the data. Concentrations of carboplatin in validation quality control samples were determined from the calibration curve and used to calculate accuracy and precision of the method within Excel (version 97, Microsoft). The measured AUC was estimated with the equation published by Sorensen et al. [17] as shown in Table 1. Predicted AUCs were calculated by the modified Calvert formula (administered carboplatin dose/(predicted CrCl or GFR + 25)).

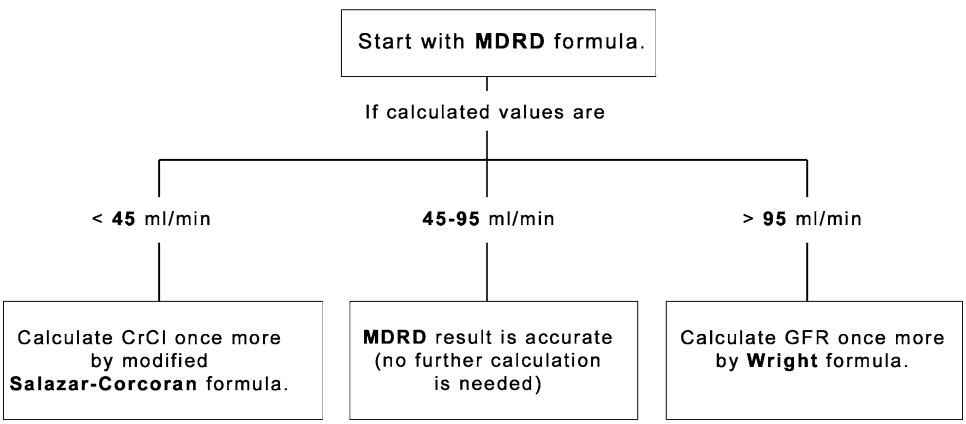

Fig. 1 Algorithm for accurate CrCl or GFR-estimation [14]

Table 1 Pharmacokinetic of carboplatin—estimation of carboplatin dose, carboplatin clearance, carboplatin AUC, BSA and estimation of renal function

Estimation of carboplatin dose	
Calvert [5]	Dose (mg) = target−AUC (mg/mL × min) × (GFR + 25) (mL/min)
Estimation of carboplatin clearance	
Chatelut [20]	Clearance (mL/min) = 0.134 × weight (kg) + (218 × weight (kg) × (1– 0.00457 × age (years) × (1– 0.314 × sex)))/SCr (μmol/L)
Schmitt [16]	Clearance (mL/min) = $117.8 \times (\text{SCr } (\mu\text{mol/L})/75)^{-0.450} \times (\text{cysC(mg/L)}/1.00)^{-0.385} \times (\text{weight(kg)}/65)^{+0.504} \times (\text{age(years)}/56)^{-0.366} \times 0.847^{\text{sex}}$
Estimation of carboplatin AUC	
Sorensen [17]	AUC (mg/mL × min) = 0.053 × $c_{0.25h}$ (mg/L) + 0.401 × $c_{2.75h}$(mg/L) + 0.628
Estimation of BSA	
DuBois [19]	BSA (m^2) = 0.007184 × weight $(kg)^{0.425}$ × height $(cm)^{0.725}$
Estimation of renal function	
oGFR	GFR (mL/min) = (administered dose (mg)/measured-AUC (mg/mL x min))−25 mL/min
Endogenous CrCl	$\text{CrCl (mL/min)} = \frac{\text{UCr(mg/dL)} \times V\text{(mL)}}{\text{SCr(mg/dL)} \times T\text{(min)}}$
Cockcroft-Gault [9]	$\text{CrCl (mL/min)} = \frac{(140 - \text{age(years)}) \times (\text{weight(kg)})}{72 \times \text{SCr(mg/dL)}} \times \text{sex}$
Jelliffe [10]	$\text{CrCl (mL/min)} = \frac{\{98 - 0.8 \times (\text{age(years)} - 20)\}}{\text{SCr(mg/dL)}} \times \left(\frac{\text{BSA}(m^2)}{1.73(m^2)}\right) \times \text{sex}$
Hoek [15]	$\text{GFR (mL/min)} = \left(-4.32 + 80.35 \times \frac{1}{\text{CysC(mg/L)}}\right) \times \left(\frac{\text{BSA}(m^2)}{1.73(m^2)}\right)$
Algorithm [14] (Fig. 1)	$\text{GFR (mL/min)} = 170 \times (\text{SCr(mg/dL)})^{-0.999} \times (\text{age(years)})^{-0.176}$
MDRD [11]	$\times (\text{sex}) \times (\text{ethnicity}) \times (\text{BU(mg/dL)})^{-0.170}$
	$\times (\text{Alb(g/dL)})^{+0.318} \times \left(\frac{\text{BSA}(m^2)}{1.73(m^2)}\right)$
MDRD < 45 mL/min	
Modified Salazar-Corcoran [12]	Males
	$\text{CrCl (mL/min)} = \frac{(137 - \text{age(years)}) \times \{(0.285 \times \text{weight(kg)}) + (12.1 \times (\text{BSA}(m^2)))\}}{(51 \times \text{SCr(mg/dL)})}$
	Females
	$\text{CrCl (mL/min)} = \frac{(146 - \text{age(years)}) \times \{(0.287 \times \text{weight(kg)}) + (9.74 \times (\text{BSA}(m^2)))\}}{(60 \times \text{SCr(mg/dL)})}$
MDRD > 95 mL/min	
Wright [13]	$\text{GFR(mL/min)} = \frac{(6580 - 388 \times \text{age(years)}) \times \text{BSA}(m^2) \times (\text{sex})}{\text{SCr}(\mu\text{mol/L})}$

Alb serum albumin, *BSA* body surface area, *BU* blood urea, *CrCl* creatinine clearance, *CysC* cystatin C, *GFR* glomerular filtration rate, *h* hour, *MDRD* modification of diet in renal disease, *oGFR* observed glomerular filtration rate, *SCr* serum creatinine, *T* time of urine collection, *UCr* urine creatinine, *V* volume of urine after 24 h

Sex: Chatelut and Schmitt male 0 female 1.0 other equations male 1.0; female Cockcroft-Gault 0.85; Jelliffe 0.9; MDRD 0.762; Wright 0.832. The MDRD formula considers the factor 1.0 if patients are white and 1.180 if patients are black

Mathematical calculation of renal function prediction

Age, ethnicity and sex were recorded. Actual body weight, height, serum creatinine, -albumin, -urea and -cystatin C were measured. BSA was calculated using the equation of DuBois and DuBois [19] (Table 1). All patients had to collect urine over 24 h for CrCl calculation before chemotherapy was started. The urine collections were compared with the last one and the difference have to be not greater than 10%. Patients were precisely instructed by trained staff. CrCl and GFR estimates were calculated in mL/min using the equations [9–15, 20] in Table 1.

Measurement of different blood and urine parameters

Blood samples were drawn during the urine collection period or in outpatients immediately afterwards to assess serum creatinine, blood urea (BU), albumin (Alb) and cystatin C. Serum and urine creatinine were measured using an alkaline picrate-kinetic assay (Jaffé) [21]. The upper limit of the serum creatinine reference interval was 1.2 mg/dL in males and 0.9 mg/dL in females and the upper limit of urine creatinine was 200 mg/dL in our laboratory. BU was determined using an urease method and expressed in milligrams per deciliter. Alb was measured

Table 2 Chemotherapy regimen, infusion duration, sampling time points, administered carboplatin dose and measured carboplatin -AUC for each patient

Nr	Sex	Chemotherapy	Infusion duration (start, end at)	Sampling point 0.25 h	Sampling point 2.75 h	Administered carboplatin dose (mg)	Measured carboplatin AUC (mg/ml × min)
1	M	Vinorelbine	1:05 h (10.12–11.17)	11.32	14.02	600	4.5
4	F	Pemetrexed	1:00 h (12.28–13.28)	13.43	16.13	385	5.2
5	F	Gemcitabine	1:00 h (10.48–11.48)	12.03	14.33	350	6.0
6	M	Paclitaxel	1:00 h (12.55–13.55)	14.10	16.40	500	6.0
8	F	Paclitaxel	1:00 h (11.35–12.35)	12.50	15.20	390	5.6
9	M	Paclitaxel/Etoposide	1:00 h (12.25–13.25)	13.40	15.10	995	5.7
10	F	Paclitaxel/Trastuzumab	1:00 h (10.35–11.35)	11.50	14.20	515	6.1
12	M	Etoposid	1:05 h (11.13–12.18)	12.33	15.03	650	4.8
13	F	Paclitaxel	1:05 h (10.30–11.35)	11.50	14.20	517	5.2
14	F	Paclitaxel	1:05 h (10.45–11.50)	12.05	14.35	568	6.6
15	F	Paclitaxel	1:00 h (12.15–13.15)	13.30	16.00	456	7.1
16	F	Paclitaxel/Trastuzumab	1:00 h (10.35–11.35)	11.50	14.20	454	5.9
17	F	Paclitaxel	1:00 h (10.45–11.45)	12.00	14.30	484	6.6
19	F	Paclitaxel	1:00 h (10.50–11.50)	12.05	14.35	406	6.7
21	F	Paclitaxel	1:00 h (10.30–11.30)	11.45	14.15	519	7.5
22	M	Etoposide	1:00 h (11.15–12.15)	12.30	15.00	600	5.8
23	F	Paclitaxel	1:00 h (10.30–11.30)	11.45	14.15	555	5.8
24	F	Paclitaxel	1:00 h (12.00–13.00)	13.15	15.45	480	5.3
25	F	Paclitaxel	1:00 h (10.30–11.30)	11.45	14.15	311	5.8
29	F	Paclitaxel	1:00 h (12.00–13.00)	13.15	15.45	560	5.1
30	F	Paclitaxel	1:00 h (10.30–11.30)	11.45	14.15	574	4.8
31	F	Paclitaxel	1:00 h (10.50–11.50)	12.05	14.35	482	4.2
32	M	Gemcitabine	1:00 h (10.30–11.30)	11.45	14.15	575	4.4
34	M	Etoposide	1:02 h (12.10–13.12)	13.27	15.57	500	6.7
35	F	Paclitaxel	1:00 h (11.10–12.10)	12.25	14.55	465	8.0
36	F	Paclitaxel	1:00 h (11.30–12.30)	12.45	15.15	375	5.7
38	F	Paclitaxel	1:00 h (11.15–12.15)	12.30	15.00	355	4.4
39	F	Etoposide	1:00 h (11.10–12.10)	12.25	14.55	470	6.7
40	F	Etoposide	1:00 h (11.20–12.20)	12.35	15.05	450	5.2

AUC area under the concentration time curve, *Nr* number of patient

using a bromcresol green method and expressed in grams per decilitre [22]. The reference intervals were 12–46 mg/dL in BU and 3.4–4.8 g/dL in Alb, respectively. Cystatin C was examined in serum samples with the N Latex Cystatin C test kit. The test represents particle-enhanced immunonephelometric method and was examined on a BN ProSpec analyser (Dade-Behring, Marburg, Germany) [23]. The reference interval for cystatin C was 0.57–0.96 mg/L in males and 0.50–0.96 mg/L in females.

Calculation of the carboplatin dose

The administered carboplatin dose was calculated by a modified Calvert formula [5] whereas GFR was substituted by CrCl via 24-h urine collection or calculated by Jelliffe [10] (Table 1). The target AUC was 5 mg/mL × min.

Statistical considerations

A sample size of at least 25 patients had to be considered for statistical analysis. The performance of the prediction of the AUCs was evaluated using the mean percentage error (MPE %, a measure of bias) and the mean absolute percentage error (MAPE %, a measure of precision) by Bland–Altman [24]. MPE was calculated as the percentage difference between the predicted AUC for each CrCl or GFR equation and measured AUC as followed:

$$\mathrm{MPE} = \left[N^{-1} \times \sum_{i=1}^{N} (\mathrm{pe}_i) \right] \times 100$$

$$\mathrm{MAPE} = \left[N^{-1} \times \sum_{i=1}^{N} (\mathrm{Ipe}_i \mathrm{I}) \right] \times 100$$

where N is the number of patients (29) and pe is the relative prediction error for predicted carboplatin AUC and it is defined as follows (predicted AUC—measured AUC) × 100/measured AUC.

An average bias close to zero was desirable. A positive bias indicated overestimation of carboplatin AUC and a negative bias indicated underestimation. The data are normally distributed, therefore statistical differences between measured and predicted carboplatin AUC were evaluated by t-test for paired samples. Results were considered to be statistically significant at $P < 0.05$.

Results

Carboplatin AUC

29 patients (22 females and 7 males) were enrolled in the analysis. Specific patient demographics, carboplatin dose, carboplatin-AUC and estimations of renal functions are detailed in Table 3. The AUC predictions of carboplatin calculated by applying the formulas are summerized in Table 4. The mean measured carboplatin was AUC 5.8 mg/ml × min (target AUC 5.0 mg/ml x min), the mean absolute administered carboplatin dose 498 mg, and the mean observed GFR (oGFR) was 63 mL/min. The bias (%) and precision (%) are displayed in Table 4. The MPE of carboplatin AUC was +5 and −5% for the Jelliffe and algorithm modified Calvert formula. The degree of bias was greater with the Cockcroft-Gault, Schmitt, Hoek, Chatelut and endogenous CrCl modified Calvert formula with the MPE being −10, −14, −15, −20, −25%, respectively.

GFR and CrCl

The mean oGFR was 63 mL/min. The Jelliffe and algorithm based renal calculation showed the lowest difference with a estimated CrCl (eCrCl) of 55 mL/min and a estimated GFR (eGFR) of 68 mL/min. All other equations showed a higher difference.

GFR and obesity

Six from 29 patients were obese with a body mass index (BMI) greater 30 kg/m^2. Data are shown in Table 5. The mean oGFR of these patients was 68 mL/min. oGFR was overestimated 1% by the algorithm and was underestimated 3% by the Jelliffe formula. The degree of bias was greater for the Cockcroft-Gault formula and the CrCl via 24-h urine collection with the MPE being +37 and +39%, respectively.

Table 3 Patients' characteristics, administered carboplatin dose, -AUC, and observed and estimated renal function

Demographic	Patients ($n = 29$) Mean ± SD
Age (years)	61.0 ± 9.0
Weight (kg)	70.5 ± 15.0
Height (cm)	167.9 ± 8.0
BSA (m^2)	1.79 ± 0.19
Carboplatin dose (mg)	
Administered	498 ± 97
Carboplatin AUC (mg/mL × min)	
Target AUC	5
Measured AUC	5.8 ± 1.0
Renal function estimations (mL/min)	
oGFR (observed GFR)	63 ± 20
eGFR (Algorithm)	68 ± 18
eCrCl (Jelliffe)	60 ± 14
eCrCl (Cockcroft-Gault)	75 ± 23
eGFR (Hoek)	79 ± 23
eCrCl (24-h urine collection)	82 ± 30

AUC area under the concentration time curve, *BSA* body surface area, *CrCl* creatinine clearance, *eCrCl* estimated creatinine clearance, *eGFR* estimated glomerular filtration rate, *oGFR* observed glomerular filtration rate, *n* number, *SD* standard deviation

GFR and renal insufficiency

A oGFR with 22 mL/min was shown by two patients (Table 5). The novel algorithm revealed the closest values to the observed situation (30 and 40 mL/min), compared to other equations, including the often in clinical practice used formula by Jelliffe (51 and 50 mL/min).

Discussion

Several recommendations clearly indicate the need for dose modification of selected anticancer drugs in patients with renal dysfunction when these drugs are excreted primarily in unchanged or active form through the kidneys [25].

According to the IRMA-1 ($n = 4{,}684$) and IRMA-2 ($n = 4{,}945$) study results which were solely based on the MDRD equation, a high prevalence of renal dysfunction should be estimated in cancer patients, when about 38–41% and 11% of patients revealed GFR values (mL/min/1.73 m^2) between 60–89 and 30–59 mL/min, respectively [26]. According to our study population these percentages may be even higher with 35% of patients being between 30 and 59 mL/min, based on GFR calculation according to the Calvert formula and carboplatin AUC measurement as well as on our novel algorithm which is not solely based on the MDRD formula [14].

Table 4 Measured carboplatin AUC (mg/mL × min) and predicted AUC by using the modified Calvert formula with estimations of renal function and administered carboplatin dose

Formula	AUC ± SD (mg/mL × min)	MPE ± SD (%)	MAPE ± SD (%)
Measured AUC	5.8 ± 1.0		
AUC—Calvert (Algorithm)	5.4 ± 1.0	−5 ± 17	15 ± 10
AUC—Calvert (Jelliffe)	5.9 ± 0.8	+5 ± 20	16 ± 13
AUC—Calvert (Cockcroft-Gault)	5.1 ± 0.9	−10 ± 17	17 ± 10
AUC—Calvert (Hoek)	4.9 ± 0.8	−15 ± 11	17 ± 9
AUC—Calvert (24-h urine collection)	4.8 ± 1.1	−25 ± 35	31 ± 30
AUC—Chatelut	4.6 ± 0.8	−20 ± 17	24 ± 11
AUC—Schmitt	4.9 ± 0.7	−14 ± 12	16 ± 8

Bias and precision between carboplatin AUC predictions and measured carboplatin AUC

AUC area under the concentration time curve, *MAPE* mean absolute percentage error, *MPE* mean percentage error, *n* number of patients, *SD* standard deviation

Table 5 Observed and estimated GFR or CrCl and AUC values in obese patients (1–6) and patients with renal insufficiency (7–8)

Nr	Sex	Age (years)	Weight (kg)	BMI (kg/m^2)	SCr (μmol)	CysC (mg/L)	Dose administered (mg)	AUC measured (mg/ml × min)	oGFR (mL/min)	eGFR (Algor) (mL/min)	eCrCl (CG) (mL/min)	eCrCl (Jelliffe) (mL/min)	eCrCl (24-h urine) (mL/min)
1	F	69	90.2	**36.1**	98	1.09	390	5.2	51	51	69	62	60
2	F	65	84.0	**30.5**	80	1.06	517	5.6	68	65	83	58	71
3	F	57	78.6	**30.7**	80	0.76	568	6.0	69	48	56	59	72
4	F	56	89.9	**33.4**	71	0.93	555	6.0	67	85	111	63	92
5	F	47	102.8	**37.8**	80	0.83	482	4.5	81	81	125	80	133
6	F	53	90.0	**30.1**	71	0.86	550	5.7	71	81	115	69	148
Mean		58	89.3	33.1	80	0.92	510	5.5	68	69	93	65	96
SD		8	8.0	3.3	10	0.13	67	0.6	10	16	28	8	37
MPE (%)										+1	+37	−3	+39
MAPE (%)										13	43	10	+39
7	F	72	50.0	17.7	106	1.69	311	6.7	**22**	30	33	51	42
8	F	67	53.6	19.9	88	1.71	375	8.0	**22**	40	46	50	42

Values in bold represent selected patients with BMI > 30 kg/m^2 or oGFR < 30 mL/min

Algor algorithmus, *AUC* area under the concentration time curve, *BMI* body mass index, *CG* Cockcroft-Gault, *eCrCl* estimated creatinine clearance, *CysC* cystatin C, *F* female, *eGFR* estimated glomerular filtration rate, *oGFR* observed glomerular filtration rate, *Nr* number, *SCr* serum creatinine

If one wants to translate the IRMA-1 and IRMA-2 study results as well as the GFR-adapted dose modifications into clinical practice, accurate assessment of the individual renal function in cancer patients will be mandatory [26]. The real situation of individual GFR is highly reflected by using radioisotopes (for example ^{51}Cr-EDTA), however, this gold standard is limited by its invasive technique, high costs, varying regulatory approvals and need for specific expertise.

The estimation of GFR by the measurement of creatinine clearance (CrCl) is a far more easy method, but needs intensified patient instruction and adherence to avoid inaccuracy and inconvenience during urine collection over 24 h in our experience. Generally, the CrCl-values overestimate GFR to some extent because of additional tubular creatinine secretion [27]. Finally, concomitant hydration of patients may bias CrCl measurement.

As a consequence, a very broad spectrum of different formulas has been published with the ambitious aim to calculate renal function in different patient populations very easily and closely to the real GFR situation [28]. In this context, formulas revealing a mean percentage error of only 1–2% compared to clearance values based on radioisotope measurements were very encouraging. However, more detailed analysis have shown a well-known difficulty with most other equations used before, namely manifest overestimation and underestimation of the "real" situation

in the GFR segments <50 ml/min and >100 ml/min, respectively [7, 8]. Based on the fact, that an overestimation of the constitutive GFR particularly in patients with renal dysfunction might result in a lower percentage of dose modifications than needed, the acceptance of novel formulas in clinical oncology remains a challenge. The same is true for the Chatelut formula, when reports about gender-dependent potential carboplatin under- and overdosing discouraged its further use [29]. Based on the well-known non-linearity of calculations over a broad range of GFR values, a novel algorithm has been recently presented by our study group based on 123 cancer patients with the aim to evaluate the probably best fitted formula for different GFR segments: <45 mL/min, 45-95 mL/min and >95 mL/min [14]. In our model, the 6-variable MDRD formula [11] resulted in an accurate estimation of GFR values between 45 and 95 mL/min, however, further calculations were needed by the modified Salazar-Corcoran formula [12] and the Wright-formula [13] in the lower and upper GFR-ranges for more appropriateness, respectively. In order to further validate the clinical usefulness of our novel algorithm, this analysis compared GFR calculated according to the Calvert formula [5] and measured carboplatin AUC, in order to compare it with different calculation methods and vice versa [9–16, 20].

Carboplatin has been widely accepted as a „model substrate" to examine clinical pharmacokinetic correlations in more detail. First, carboplatin reflects a fairly simple clinical pharmacokinetic behaviour because about 75% of the applied dose are excreted in the urine whereas the remainder is primarily bound to different tissues from which it may be released very slowly over time [1, 5]. Second, AUC values are clinically relevant and have been shown to correlate with the probability of response as well as the risk for severe forms of thrombocytopenia [2, 3]. Third, AUC values can be measured in vivo without the need for multiple blood sampling [17, 30]. According to the Calvert formula (carboplatin dose = target AUC × [GFR + 25]) [5], GFR can be calculated by the ratio, administered carboplatin dose/measured AUC − 25.

Based on our study results the use of the MDRD formula may be favoured for cancer patients between 45 and 95 mL/min which is in accordance to other study groups who found a closer correlation of MDRD-related estimates to measured ^{125}I-iothalamate and aminoglycoside clearance than with other calculations particularly in patients with chronic kidney disease [31]. Conflicting data were primarily based on observational study results, referring on clinical end points (for example carboplatin-associated nadir of thrombocytopenia during early treatment cycles) rather than clinical-pharmacokinetic data.

Our study results revealed some further important information when we compared GFR assessment by the novel algorithm [14] based on carboplatin AUC measurements compared to other estimations [9, 10, 15, 16, 20].

1. In contrast to the algorithm-based values, most obese patients with a body mass index (BMI) ranging from 30.1 to 37.8 kg/m^2, GFR values calculated by the CG-formula were clearly overestimated, as well as CrCl via 24-h urine collection.
2. CrCl assessment via 24-h urine collection can be associated with enormous deviations up to 138 mL/min in individual patients, which may be related to bias via intensified hydration, whereas concomitant hydration did not have an impact on the results revealed by the novel algorithm.
3. In two patients with oGFR values below 30 mL/min (both 22 mL/min) the novel algorithm revealed the closest values to the measured situation (30 and 40 mL/min), compared to other equations, including the Jelliffe formula (51 and 50 mL/min).
4. Compared to the Hoek formula which include cystatin C measurement as a further parameter to increase accuracy, we observed a lower mean percentage error (MPE) with the novel algorithm.

Although cystatin C may be a more sensitive marker than serum creatinine to assess individual GFR because of the neglectable role of gender, muscle mass or age-related factors, those results are primarily derived from healthy volunteers, whereas in cases of inflammation, concomitant application of prednisone and diabetes mellitus, deviations are highly probable to occur resulting in underestimation of GFR [27]. In addition, cancer patients may have an enhanced extracellular secretion of cysteine proteases in different tumor types which results in an increase of cystatin C accompanied by potential GFR overestimation [32].

Our suggestion to prefer the MDRD formula [11] rather than a cystatin C-based equation (for example Hoek formula) [15] in a broad spectrum of patients with GFR > 60 ml/min/1.73 m^2 is supported by the results of a comparative trial in former kidney donors when the MDRD equation revealed to be more accurate than the latter with iohexol GFR as a reference [33].

Based on these findings the enthusiasm was based on presentation of a universal formula for the calculation of carboplatin clearance [16] irrespective of the underlying body weight of the patient (for example 40–137 kg) may have to be restrained. In our study population, the retrospective use of this universal formula did not result in closer values to carboplatin AUC based on the Calvert formula than our novel algorithm.

Though the concept to use the novel algorithm for accurate GFR calculation in clinical practice is clearly encouraged by the study results, there may be some limitations: first, one may argue that far more cancer patients

may be needed to validate MPE (%) and MAPE (%) more extensively and, second, a correlation of GFR values revealed by radioisotope measurements rather than calculations via the modified Calvert formula and carboplatin AUC measurement may prove the practicability of the novel algorithm more tightly. Third, we used a limited sampling method which need a strictly controlled infusion duration and blood sampling points of each patient. Fourth, patients with special conditions, for example very low serum creatinine values, may need modified GFR estimation for example based on body cell mass, to improve dose individualization [34].

In conclusion, the presented study results based on carboplatin AUC measurements indicate that the concept to find one single formula to calculate accurately individual GFR values over a broad range of constitutive renal function may be less successful than an algorithm-based strategy which does not include cystatin C as a further parameter.

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