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Cockcroft-Gault, Modification of Diet in Renal Disease, and Chronic Kidney Disease Epidemiology Collaboration equations for estimating glomerular filtration rates in cancer patients receiving cisplatin-based chemotherapy

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Background: Although the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation has been recommended for accurate estimates of glomerular filtration rate (eGFR), there is little information regarding differences in GFR estimates obtained using the Cockcroft-Gault (CG) or Modification of Diet in Renal Disease (MDRD) equations in East Asian cancer patients. We investigated discrepancies in GFR and toxicities in patients treated with cisplatin-based chemotherapy using three equations equations.

Methods: A total of 229 patients were retrospectively recruited. We calculated eGFR using the three equations and separated patients into three categories based on GFR < 10 (group A), 10–50 (group B), and > 50 (group C) mL/min/1.73m^2. We analyzed chemotherapy toxicities.

Results: The mean eGFR calculated using the CG was the lowest of the values derived using the three equations. Estimates using the MDRD and CKD-EPI equations resulted in reclassifying 32 (71.1%) and 33 (73.3%) of 45 patients, originally placed in group B using the CG into group C. However, only 1 (7.7%) of 13 patients placed in group B using the MDRD were reclassified into group C using the CKD-EPI. Twenty-eight of 45 patients classified into group B using the CG equation were treated with reduced doses of cisplatin. However, these patients did not show significant differences in toxicities compared with other patients taking full doses of cisplatin.

Conclusion: The CG equations underestimated GFR compared to the MDRD and CKD-EPI equations. Therefore, when GFR is estimated using CG equations, East Asian cancer patients may receive insufficient doses of chemotherapeutic agents, including cisplatin.

Keywords: Cisplatin, Chronic Kidney Disease Epidemiology Collaboration equation, Glomerular filtration rate

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Introduction

Cisplatin is a widely used chemotherapeutic agent for the curative and/or palliative treatment of several cancers. The excretion and nephrotoxicity of cisplatin depends on renal function [1]. Therefore, accurate estimates of renal function in patients receiving cisplatin-based chemotherapy are essential for determining drug doses, predicting adverse effects, interpreting signs and symptoms after administration, and surveillance of acute kidney injury. Although glomerular filtration rate (GFR), which is based on the clearance of exogenous markers like inulin, ^{51}Cr-EDTA, and iohexol, is considered the best overall index of renal function, it is difficult to measure in clinical practice. Instead, estimates of GFR (eGFR) are calculated using equations that are based on serum creatinine (SCr) levels, such as the Cockcroft-Gault (CG), Modification of Diet in Renal Disease (MDRD), and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations [2–4]. Although similar clinical variables, such as age, gender, SCr, and ethnicity have been used to calculate eGFR, the CKD-EPI equation has recently been established as the most accurate method through validation studies [5,6]. In addition, the CKD-EPI equation has been recommended due to possible inaccuracies of eGFR estimates made using CG or MDRD equations in East Asian populations or in patients with renal insufficiency [7,8]. However, current chemotherapeutic regimens are mainly based on eGFR estimates derived using CG or MDRD equations, and there is little information regarding estimates of eGFR calculated using different equations in cancer patients, especially within the East Asian population. Therefore, we investigated discrepancies in toxicities and eGFR estimates calculated using different equations in East Asian cancer patients treated with cisplatin-based chemotherapy.

Methods

Patients

We retrospectively enrolled patients who received cisplatin-based systemic chemotherapy at the Division of Hematology-Oncology, Department of Internal Medicine, Jeju National University Hospital between April 2009 and May 2014. To accurately represent renal function prior to chemotherapy and toxicities resulting from chemotherapy, we excluded patients who 1) received first cycles of chemotherapy at a different institution; 2) were treated with chemoradiotherapy; 3) were receiving renal replacement therapy (hemo or peritoneal dialysis); 4) were treated with reduced-dose chemotherapy, except for patients with renal dysfunction defined by the CG equation; 5) had unknown renal function prior to chemotherapy; and 6) had undetermined chemotherapy toxicities due to lack of follow-up. Following these exclusion criteria, a total of 148 patients were excluded (no first cycle chemotherapy in 35 patients, chemoradiotherapy in 40 patients, receiving hemodialysis in 2 patients, dose reduction for other causes except renal dysfunction in 55 patients, unknown renal function in 1 patient, and lack of follow-up after chemotherapy in 15 patients). Finally, a total of 229 patients who received cisplatin-based chemotherapy were recruited for this retrospective study.

We collected demographic and clinical data including age, gender, height, weight, body surface area (BSA), body mass index (BMI), performance status, cancer diagnosis, purpose of chemotherapy (curative, adjuvant/neoadjuvant or palliative), and cisplatin dosage. BSAs were calculated using the Mosteller formula: $\sqrt{\frac{\text{height(cm)} \times \text{weight(kg)}}{3{,}600}}$ [9]. BMIs were calculated as $\frac{\text{body weight (kg)}}{\text{height (m)} \times \text{height (m)}}$ [10]. Patients were divided into four subgroups based on BMI following the international classification of the World Health Organization: underweight (< 18.50 kg/m^2), normal (18.50–24.99 kg/m^2), overweight (25.00–29.99 kg/m^2), and obese (≥ 30.00 kg/m^2) [10]. The present study was approved by the Institutional Review Board of Jeju National University Hospital (IRB No. 2014-05-016).

Estimation of GFR

eGFR was calculated according to the CG, MDRD, and CKD-EPI equations using the following formulas based on SCr (mg/dL) [2–4]. Baseline SCr used the latest Cr measured within 7 days before the patient's first cisplatin-based chemotherapy. SCr was determined by the kinetic Jaffe method using Creatinine FS reagent (DiaSys Diagnostics, Holzheim, Germany) and an automated chemistry analyzer (Toshiba 200FR; Toshiba, Tokyo, Japan). The calibration was not isotope-dilution mass spectrometry-traceable. We calculated CG adjusted for

BSA using body weight in kg prior to chemotherapy.

(1) CG equation: $\{[1.73 \times (140 - \text{Age}) \times \text{body weight}] / (72 \times \text{SCr} \times \text{BSA})\} \times 0.85$ (if female)

(2) MDRD equation: $186 \times (\text{SCr})^{-1.154} \times (\text{Age})^{-0.203} \times 1.212$ (if black) $\times 0.742$ (if female)

(3) CKD-EPI equation:

Female with SCr ≤ 0.7: $144 \times (0.993)^{\text{Age}} \times (\text{SCr}/0.7)^{-0.329}$

Female with SCr > 0.7: $144 \times (0.993)^{\text{Age}} \times (\text{SCr}/0.7)^{-1.209}$

Male with SCr ≤ 0.9: $141 \times (0.993)^{\text{Age}} \times (\text{SCr}/0.9)^{-0.411}$

Male with SCr > 0.9: $141 \times (0.993)^{\text{Age}} \times (\text{SCr}/0.9)^{-1.209}$

Cisplatin dosing and chemotherapy toxicity

Physicians made decisions regarding whether to administer reduced or full doses of cisplatin to patients based on renal function as calculated using the CG equation. We evaluated hematologic and non-hematologic toxicities, including nephrotoxicity, associated with chemotherapy after the first cycle according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTACE) Version 4.0 [11].

Statistical analyses

Chi-square or Fisher's exact tests were used to compare toxicities according to eGFR categories. The Friedman test was used to determine differences between renal function estimates derived using the CG, MDRD, and CKD-EPI equations. Cochran's Q or McNemar's tests were used to determine differences in eGFR groupings among these equations. All analyses were performed using PASW Statistics software (ver. 18.0; IBM Co., Armonk, NY, USA). Statistical significance was set at 2-tailed $P < 0.05$.

Results

Baseline characteristics

The baseline characteristics of the enrolled patients are summarized in Table 1. There were 156 males and 73 females included in this study. The mean age was 60 years. The mean BSA and BMI were 1.64 m^2 and 22.9 kg/m^2, respectively. The mean initial SCr was 1.0 mg/dL. Gastrointestinal tract cancer was the most common diagnosis (37.9%), followed by lung cancer (34.3%). Of the 229 patients included in the sample, 185 (80.8%) received palliative chemotherapy.

Table 1. Baseline characteristics of enrolled patients

Variable	Patient (n = 229)
Age (yr)	60 ± 10
< 50	28 (12.2)
50–59	74 (32.3)
60–69	79 (34.5)
70–79	43 (18.8)
> 80	5 (2.2)
Sex, male	156 (68.1)
BSA (m^2)	1.64 ± 0.17
BMI (kg/m^2)	22.9 ± 3.5
Underweight/normal	20 (8.7)/150 (65.5)
Overweight/obese	54 (23.6)/5 (2.2)
ECOG performance status	
0–1/2–3	120 (52.4)/47 (20.5)
Unknown	62 (27.1)
Underlying malignancy	
Lung cancer	
NSCLC/SCLC	63 (27.5)/16 (7.0)
Gastrointestinal tract cancers	
Esophageal/gastric cancer	22 (9.6)/29 (12.7)
Pancreas/biliary tract cancer	11(4.8)/25 (10.9)
Head and neck cancer	20 (8.7)
Breast cancer	17 (7.4)
Gynecology cancers	
Cervix/ovary/other cancers	5 (2.2)/3 (1.3)/2 (0.9)
Bladder cancer	3 (1.3)
Other cancers	13 (5.7)
Chemotherapy	
Curative	6 (2.6)
Adjuvant/neoadjuvant	37 (16.2)/1 (0.4)
Palliative	185 (80.8)
1st/ 2nd/ ≥ 3rd line	134 (72.4)/31 (16.8)/20 (10.8)
Initial SCr (mg/dL)	1.0 ± 0.21
eGFR equation	
CG	67.40 ± 17.58
MDRD	75.82 ± 18.51
CKD-EPI	75.83 ± 16.65

Data are presented as mean ± standard deviation or number (%).

BMI, body mass index; BSA, body surface area; CG, Cockcroft-Gault; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; ECOG, Eastern Cooperative Oncology Group; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; SCr, serum creatinine.

$P < 0.01$.

Comparisons of eGFRs using the CG, MDRD and CKD-EPI equations, according to cisplatin dosing guidelines

The mean eGFR calculated using the CKD-EPI equation was the highest among the three equations, and the differences between each eGFR estimate were statistically significant (mean eGFR: CG vs. MDRD vs. CKD-EPI = 67.40 vs. 75.82 vs. 75.83, respectively; Friedman test, $P < 0.001$) (Table 1). Based on cisplatin dosing guidelines, we categorized patients into three groups for each of the three equations: eGFR < 10 mL/min/1.73m^2, eGFR = 10–50 mL/min/1.73m^2, and eGFR > 50 mL/min/1.73m^2 (Table 2) [12]. No patients were identified by any equation to have an eGFR < 10 mL/min/1.73m^2.

Of the total 229 patients, 45 (19.7%), 13 (5.7%), and 12 (5.2%) patients were classified into the group with eGFR = 10–50 mL/min/1.73m^2 by the CG, MDRD, and CKD-EPI equations, respectively.

The CG equation placed a significantly greater proportion of patients into this group compared to the MDRD and CKD-EPI groups (Cochran's Q test, $P < 0.001$). The differences among the three equations were consistent regardless of gender, BMI (underweight and normal vs. overweight and obese), and age group (50–59, 60–69, 70–79, and > 80 years) except for the youngest patients (< 50 years) ($P < 0.001$).

Of the total 45 patients with eGFR of 10–50 mL/min/1.73m^2 as calculated using the CG equation, 32 (71.1%) and 33 (73.3%) patients were reclassified to the eGFR > 50 mL/min/1.73m^2 group using the MDRD and CKD-EPI equations, respectively.

Additionally, 1 of 13 (7.7%) patients with an eGFR of 10–50 mL/min/1.73m^2 as calculated using the MDRD equation was reclassified into the eGFR > 50 mL/min/1.73m^2 group using the CKD-EPI equation.

Therefore, the overall concordance rates were 86.0% between the CG and MDRD equations, 85.5% between the CG and CKD-EPI equations, and 99.5% between the MDRD and CKD-EPI equations.

Analysis of patients with eGFR 10–50 mL/min/1.73m^2 estimated by the CG equation

Among the 45 patients with eGFR of 10–50 mL/min/1.73m^2 as calculated using the CG equation, 28 (62.2%) patients received reduced cisplatin doses (reduction rate, 15–50% from original dose) as determined by their physicians. Mean eGFR in patients treated with reduced dosage was significantly lower than in patients treated with full doses (mean 43.33 vs. 46.38; *t*-test, $P = 0.042$). Of these 28 patients, 20 (71.4%) were classified as eGFR > 50 mL/min/1.73m^2 by the MDRD equation and 18 (64.3%) were classified as eGFR > 50 mL/min/1.73m^2 by the CKD-EPI equation.

Chemotherapy toxicities were compared between the reduced-dose group and full-dose group with eGFR of 10–50 mL/min/1.73m^2 as calculated using the CG equation. There were no significant differences in hematologic toxicities between the two groups. The proportions of the reduced-dose group vs. that of the full-dose group with hematologic toxicity greater than Grade 3 were, respectively: leukopenia, 14.2% vs. 17.6% ($P = 0.49$); neutropenia, 28.5% vs. 23.5% ($P = 0.24$); thrombocytopenia, 7.1% vs. 5.8% ($P = 0.84$); anemia, 35.7% vs. 35.2% ($P = 0.75$). Gastrointestinal toxicities were not significantly different between the two groups. The proportions of the reduced-dose group vs. the full-dose group with gastrointestinal toxicity greater than Grade 3 were, respectively: nausea, 10.7% vs. 5.8% ($P = 0.58$); vomiting, 3.5% vs. 5.8% ($P = 0.83$); diarrhea, 14.2 % vs. 17.6 % ($P = 0.21$); and mucositis, 7.1 % vs. 0.0% ($P = 0.53$). Nephrotoxicity greater than Grade 1 occurred in 14.2% vs. 17.6% of the reduced-dose and full-dose groups, respectively. This difference was not significant ($P = 0.53$).

Table 2. Comparisons of eGFR using CG, MDRD and CKD-EPI equations, according to cisplatin dosing guidelines

eGFR	MDRD (n = 229)		CKD-EPI (n = 229)		*P* value
	10–50 (n = 13)	> 50 (n = 216)	10–50 (n = 12)	> 50 (n = 217)	
CG (n = 229)					< 0.001*
10–50 (n = 45)	13	32	12	33	
> 50 (n = 184)	0	184	0	184	
MDRD (n = 229)					1.000†
10–50 (n = 13)			12	1	
> 50 (n = 216)			0	216	

CG, Cockcroft-Gault; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease.

*Cochran's Q test, †McNemar's test.

Discussion

In this study, we compared eGFR calculated using three different equations (CG, MDRD and CKD-EPI) in Korean cancer patients. Although accurate estimation of GFR is important for determining the dosages of chemotherapeutic agents including cisplatin due to its narrow therapeutic range, there is little information to help clinicians use the most appropriate equation for calculating eGFR in cancer patients. The few previous studies have mainly focused on genitourinary or gynecologic cancers, and exclusively examined Western patients [13–16]. Traditionally, the CG equation, which considers age, gender, body weight, and SCr, is used to estimate GFR due to its simplicity and convenience. However, strong links between SCr and muscle mass, tubular secretion, and ethnicity have been identified, and therefore the MDRD equation was developed to include ethnic corrections (white vs. black) [17–20]. More recently, the CKD-EPI equation was developed to reflect other ethnic factors and to consider the results of epidemiological trials on CKD prevalence. The CKD-EPI equation is currently considered to be the most accurate method for estimating GFR based on validation studies [5,6,21]. Matsushita et al [5] reported that the CKD-EPI equation resulted in better risk categorization compared to the MDRD equation in a study of more than 1 million participants residing in 40 countries/regions. They also demonstrated correlations between subgroups defined by age, sex, and ethnicity. Furthermore, several studies demonstrated the accuracy of eGFR estimates made using the CKD-EPI equation in disease groups with stroke, heart failure, or CKD [5,6,8,21].

In the present study, we also observed significant discrepancies between eGFRs calculated using the three equations (CG, MDRD, and CKD-EPI) according to cisplatin dosing guidelines. The mean eGFR calculated using the CDK-EPI equation was higher than that calculated using the CG equation, but was similar to that calculated using the MDRD equation. More than 70% of patients classified into the mid-range eGFR group (10–50 mL/min/1.73m^2) by the CG equation were reclassified into the higher eGFR group (> 50 mL/min/1.73m^2) by the MDRD and CKD-EPI equations. However, only 7% of patients that were classified into the mid-range eGFR group by the MDRD equation were reclassified into the higher eGFR group by the CKD-EPI equation. Interestingly, no patients were reclassified into a lower eGFR group by the MDRD or CKD-EPI equations compared to classifications made using the CG equation. Therefore, our results confirm that traditional estimates using the CG equations may underestimate renal function and lead to insufficient administration of chemotherapeutic agents in some cancer patients. Although there is controversy as to whether the MDRD equation can be accurately used for patients with GFR > 60 mL/min/1.73m^2, other studies have reported that the MDRD equation underestimates true GFR at levels > 60 mL/min/1.73m^2 and may therefore lead to the misdiagnosis of healthy people as being in early stage CKD [22,23]. However, we observed no significant differences in patients with eGFR 10–50 mL/min/1.73m^2 and > 50 mL/min/1.73m^2 compared with those classified using the CKD-EPI equation.

Among the 45 patients with eGFR 10–50 as calculated by the CG equation, only 28 (62.2%) patients received reduced dose chemotherapy. Although we expected that patients with GFR 10–50 mL/min/1.73m^2, who received the full dose of cisplatin, would show higher chemotherapy toxicities compared to those who received reduced doses of cisplatin, there were no significant differences between the two groups. These results may be explained by small sample size or the better performance status of patients receiving full dose chemotherapy.

Our study has several limitations. First, eGFR estimates calculated by each equation were not compared with gold standard measurements using inulin, 51Cr-EDTA, or iohexol clearance. However, this gold standard is cumbersome to adjust in clinical settings. Second, since all of the patients in this study were ethnic Koreans, it may be problematic to generalize our results across other ethnic groups. Third, only a subset of patients who had eGFR 10–50 mL/min/1.73m^2 according to the CG equation were treated with reduced doses of cisplatin, and rate reduction varied from 10% to 50%. Thus, it was difficult to accurately determine the relationship between eGFR and chemotherapy toxicity. However, this difficulty reflects clinical practices of physicians in the real world. Fourth, additional variables that could affect eGFR or toxicities, including the use of other chemotherapeutic agents combined with cisplatin, nephrotoxic agents such as nonsteroidal anti-inflammatory drugs, and hydration status, were not fully evaluated.

Several studies have shown that CG equations for cal-

culating eGFR may underestimate eGFR compared to the MDRD or CKD-EPI equations. This discrepancy suggests that inadequate doses of chemotherapeutic agents are sometimes administered to cancer patients. Therefore, it is important that further validation studies are performed to determine the most accurate method of representing GFR in East Asians and other populations or ethnic groups. Accurate eGFR estimates can help guide oncologists to make more successful decisions when treating cancer patients.

In the present study, CG equations underestimated eGFR compared to the MDRD and CKD-EPI equations in Korean cancer patients who received cisplatin-based chemotherapy. Therefore, estimates of eGFR determined using CG equations may lead to the administration of insufficient doses of cisplatin and other chemotherapeutic agents to Korean cancer patients, and are not useful for limiting cisplatin. Further validation studies are required to identify the most accurate method for represents GFR in East Asian cancer patients.

Conflicts of interest

All authors have no conflicts of interest to declare.

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