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Association Between Renal Function and Chemotherapy-Related Toxicity in Older Adults with Cancer

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Abstract

Purpose—To evaluate the association between renal function (RF) and chemotherapy-related toxicity (CRT) in older adults with cancer and to compare the effect of different RF formulas and body weight measurements on this association.

Methods—This is a secondary analysis of data from a prospective multicenter study of patients age 65 who were starting a new chemotherapy regimen. RF was estimated with 4 formulas (modified Jelliffe [Jelliffe], Cockcroft-Gault [CG], Wright, and Modification of Diet in Renal Disease [MDRD]), using actual, ideal and adjusted body weights for 492 patients. The association between baseline RF and grade 3–5 CRT was evaluated by unconditional logistic regression.

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All remaining authors have declared no conflicts of interest.

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Results—As a continuous variable, decreased creatinine clearance (CrCl) calculated by CG with actual body weight was associated with increased odds of CRT (OR 1.12, $P<0.01$; 95% CI 1.04–1.20) indicating that on average for every 10 mL/min decrease in CrCl the odds of CRT increased by 12%. Very low RF (in the lowest 10%) with all formulas (CG, Jelliffe, Wright and MDRD) was associated with increased odds for CRT. This association is independent of the type of chemotherapy received (those requiring dose adjustment for renal function vs not). Neither primary dose reduction nor chemotherapy duration was associated with CRT. Serum creatinine alone was not associated with increased odds of CRT (OR 0.67, $P=0.15$).

Conclusions—Decreased RF is associated with increased odds of CRT and should be considered when assessing risk of CRT in older adults with cancer. Serum creatinine alone is not adequate for risk assessment.

Keywords

Renal function; Chemotherapy toxicity; Older Adults; Creatinine Clearance

INTRODUCTION

Adults age 65 and older comprise over half of new cancer diagnoses in the United States annually [1]. This population presents unique management challenges as there is an age-associated increased risk for chemotherapy-related toxicity (CRT) [2]; however, the aging process is heterogeneous and the factors contributing to that risk are being defined [3, 4]. Multiple studies have demonstrated the efficacy of systemic chemotherapy in older adults [5, 6]. Treatment decisions should not be made on chronologic age alone and better metrics are needed to identify those at risk for CRT. Age-related physiologic changes such as decline in renal function (RF) represent potential risk factors for increased CRT.

As many chemotherapy agents undergo renal clearance and require dose adjustment with renal insufficiency, treating clinicians are routinely calculating their patients' RF. Although serum creatinine (sCr) is simply and quickly obtained, this value alone is not an adequate indicator of RF in older adults [3, 7], as many older adults with a normal sCr have some degree of impaired glomerular filtration [8–10]. Formulas to assess RF either by calculated creatinine clearance (CrCl) or estimated glomerular filtration rate (GFR) give a quick and more reliable estimate of RF than sCr alone [11–14]. However, several such formulas exist, each with their own unique advantages and disadvantages, with some utilizing patient weight and others not [15]. Despite recommendations from the International Society of Geriatric Oncology (SIOG) to calculate RF with either Modification of Diet in Renal Disease (MDRD) or Cockcroft Gault (CG) [16], multiple formulas are routinely used in practice for estimating RF and dosing chemotherapy. Actual body weight (ABW) is the intended weight variable in these formulas, however, in practice clinicians often utilize ideal or adjusted body weight (AjbW), out of concern for either underestimating or overestimating RF. Clinicians lack guidance as to which formula may identify patients at increased risk for CRT (as well as whether actual, ideal, or AjbW should be utilized [17–19]).

The primary goals of this study are to examine the association between RF, as measured by CrCl and GFR, and CRT among older adults with cancer and to identify which RF formula best demonstrates this association, including whether actual, ideal or A₂BW should be utilized in the calculation. Answering these questions will provide practical information for clinicians assessing RF in older patients in order to identify patients at greater risk for CRT.

Patients and Methods

The prospective multicenter study “Determining the Utility of an Assessment Tool for Older Adults with Cancer” conducted by the Cancer and Aging Research Group (CARG) [3] assessed 500 older adults with cancer to identify risk factors and a predictive model for CRT. Patients with cancer starting a new outpatient chemotherapy regimen, aged 65 and older were eligible (See Table S1 for regimens received). Patients were enrolled at seven institutions between November 2006 and November 2009. The institutional review board at each institution approved the study. All patients completed an informed consent. In this study we retrospectively analyzed these data to evaluate the association between RF, as measured by calculated CrCl and estimated GFR, and CRT.

Study Schema

Prior to starting chemotherapy, patients completed an assessment that included geriatric assessment (GA) variables and socio-demographics. The GA consisted of both provider and patient reported sections and evaluated the domains of functional status, social support, comorbidity, medications, nutrition and psychological state. Details of the measures included in this assessment have been previously published [20].

Tumor and treatment variables as well as laboratory test results (including sCr) were documented. Characteristics of the treatment regimen including the drugs received, the line of chemotherapy (first line or greater), the use of growth factors (both for primary prevention and secondary prophylaxis) and dose reductions were recorded.

Patients were followed from prior to initiation of a new chemotherapy regimen until the completion of their chemotherapy course. Grade 3 (severe), 4 (life-threatening) and 5 (fatal) toxicities as defined by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 3.0 were captured at each visit and subsequently verified by a two physician review.

Methods and Statistical Analysis

In the original study, descriptive analyses were performed to summarize patient, tumor and treatment characteristics and GA results. The incidence of NCI CTCAE grade 3–5 toxicities were recorded and grouped into hematologic and non-hematologic toxicity.

- Four formulas that assess RF were evaluated: CG [11], modified Jelliffe (Jelliffe) [12, 21], Wright [14], and MDRD [13]. CG and Jelliffe estimate CrCl whereas Wright and MDRD estimate GFR; CG utilizes patient weight directly, Wright and Jelliffe incorporate weight with body surface area (BSA). MDRD does not directly take patient weight into account but rather normalizes the result to an

average BSA of 1.73 meters squared, to minimize variation due to height and weight and to allow for comparison between individuals with different body size [22]. RF was calculated for all patients with each formula and with each of the 3 different weight values (actual, ideal [23] and adjusted [24, 25]) as applicable (ideal body weight was calculated as: $50\text{kg} + (2.3\text{kg} * (\text{height in inches} - 60))$ for male and $45.5\text{kg} + (2.3\text{kg} * (\text{height in inches} - 60))$ for female; AjbW was calculated as $0.3 * (\text{actual body weight} - \text{ideal body weight}) + \text{ideal body weight}$. The estimated CrCl and GFR by each formula and serum creatinine were ranked and deciles were used to categorize patients into 10 groups. Dichotomized variables were created to compare patients in the lowest 10% of CrCl/GFR vs. the rest. Chemotherapy drugs were stratified by the following categories (Table S1): platinum-based regimens, regimens containing any drug requiring dose-adjustment for renal dysfunction (according to the package insert), and regimens with only drugs not requiring dose adjustment for renal dysfunction (according to the package insert).

Mean (std), median and range of CrCl and GFR were calculated. Logistic regression was used to evaluate the association between each of the different measures of RF, including sCr, and grade 3–5 CRT. Our dependent variable was whether a patient experienced any grade 3–5 toxicity, and our independent variables included: 1) continuous variables for RF calculated by each of the formulas, using actual, ideal and AjbW as applicable and serum creatinine; 2) four level ordinal variables created using 30, 60 and 90 as cutoff points; 3) and dichotomized variables comparing the lowest 10% vs. the rest. In 2011, we published a predictive model for grade 3 to 5 toxicity and a risk scoring system was developed including CrCl as one of the components. The original risk score included the Jelliffe formula using ideal body weight, where a weight of “3” is assigned if the CrCl is less than 34. In this analysis, we also tested the effect of the other formulas (using a CrCl < 34 as the cutoff point with “3” as the assigned weight) by evaluating the discrimination of the risk score models by calculating the area under the receiver operation characteristic (ROC) curve. As secondary analyses, we tested whether primary dose reduction or duration of chemotherapy (measured in weeks) was correlated with toxicity in our models. Type I error level of 0.05 was used as the level for determining statistical significance. All statistical analyses were done by using SAS 9.2 (SAS Institute, Cary, NC) and STATA SE 12.0 (StataCorp, College Station, Texas).

Results

Patients, Drugs Received and Treatment Toxicity

The original cohort consisted of 500 patients, of which 492 patients had the data required to assess RF by the formulas examined (Table 1). The mean age of patients was 73 (range 65–91), with 40% of patients age 75 years or older, and 18% between the ages of 80 and 91. All stages of cancer (I–IV) were represented, with 62% having stage IV disease. The majority of patients (75.4%) received chemotherapy drugs that require dose adjustment based on RF. Forty-five percent of patients had a normal body mass index (BMI 20–25), 31% were overweight (BMI 25–30) and 19% were obese (BMI > 30). For the majority of patients (87%), their ABW was above their ideal body weight (IBW); 218 patients' ABW was 30% over their ideal body weight.

One or more grade 3–5 toxicities occurred in 53% of patients (26% experienced a hematologic toxicity and 43% experienced a non-hematologic toxicity). The most common hematologic toxicities were cytopenias (11% neutropenia, 10% leukopenia, 10% anemia). The most common non-hematologic toxicities were fatigue (16%), infection (10%) and dehydration (9%).

Renal Function

The mean CrCl and GFR of the 492 patients using Jelliffe, CG, Wright and MDRD formulas, with actual, ideal and AjBW calculations as applicable, are shown in Table 2. Compared to the ABW calculations, mean CrCl and GFR values with ideal and AjBW are similar (Table 2). However, there is a larger difference between the ABW mean CrCl and the ideal and AjBW means for CG in comparison to other formulas. The number of patients with renal function values (<30 mL/min, 30–59 mL/min, 60–89 mL/min, or 90 mL/min) by each formula and body weight calculation utilized are shown in (Table 3). Patients with estimated CrCl or GFR less than 30 ranged from 2.4% (MDRD) to 8.7% (CG with ideal BW); greater than 90 ranged from 5.1% (Jelliffe with ideal BW) to 29.1% (Wright with ABW).

Association Between Renal Function and Chemotherapy-Related Toxicity

There was no association between sCr alone and the probability of grade 3–5 toxicity (OR 0.67, $P=0.15$). There was an association between decreased RF and CRT when RF was estimated by calculated CrCl using CG with ABW (OR 1.12, $P<0.01$ 95% CI 1.04–1.20). This indicates that on average for every 10 mL/min decrease in CrCl (for example a decrease from 60 mL/min to 50 mL/min), the odds of developing grade 3–5 toxicity is 12% higher (Table 4). Although the p -values did not meet statistical significance, the ORs for the non-CG formulas were all in the same direction (indicating increased risk of CRT with decreasing RF), and were similar in magnitude (1.03 MDRD, 1.06 Wright, 1.09 Jelliffe) (Table 4). We tested whether primary dose reduction or duration of chemotherapy (measured in weeks) was correlated with toxicity. These were both assessed as univariate factors, and as covariates in multivariate models that included each of the CrCl calculations. Neither primary dose reduction nor chemotherapy duration was associated with toxicity in either set of models.

In a separate analysis, we considered CrCl as an ordinal independent value. Compared to a reference group with CrCl >90mL/min (by CG with ABW) those with lower CrCl had higher odds of toxicity (OR 1.42, 95% CI 0.89–2.28, $P=0.14$ for CrCl 60–89; OR 1.74, 95% CI 1.05–2.89, $P=0.03$ for CrCl 30–59; OR 3.50, 95% CI 1.27–9.65, $P=0.02$ for CrCl <30). We also used deciles to categorize patients into 10 groups (highest to lowest RF). Results showed that at very low levels of RF (the lowest 10%), all formulas showed an association with increased odds of CRT (Table 5), but only CG with ABW showed this association across the continuum of RF values. All four formulas demonstrated similar discrimination in predicting chemotherapy related toxicities when they were incorporated into the Cancer and Aging Research Group chemotherapy toxicity calculator [4] utilizing a CrCl or GFR cutoff of <34 (ROC of the AUC ranged from 0.71 to 0.72).

We tested the hypothesis that the relationship between RF and toxicity is dependent on the type of chemotherapy received. We partitioned the treatment regimens into three categories: platinum-based regimens, regimens which contained any drug requiring dose-adjustment for renal dysfunction, and regimens with only drugs that do not require dose adjustment for renal dysfunction. In each of these chemotherapy-partitioned cohorts, we calculated the odds ratio (OR) and tested for statistical associations. There was a consistent relationship between decreased RF and increased odds of CRT for patients in each of these categories (Tables S2–S4).

Discussion

This study found an association between decreased RF and increased odds of CRT. For every 10 mL/min decrease in CrCl there was a 12% increase in odds for grade 3–5 CRT, when CrCl is calculated by CG using ABW. This finding reinforces the importance of calculating CrCl to identify older adults at increased odds for CRT, as opposed to relying on sCr alone, which neither accurately reflects RF as calculated by CrCl or GFR, nor as shown in this study, correlates with the odds of experiencing CRT.

These results provide guidance as to how to best estimate RF for the purpose of assessing toxicity risk in this population. Although the OR for all formulas examined demonstrate a similar relationship between decreased RF and increased probability of CRT, only the OR for the CG formula (using ABW) met statistical significance. The CARG predictive model for CRT developed from the original study that served as the data set for this analysis utilized Jelliffe with IBW (with a cutoff of CrCl <34 mL/min) [3, 4]. Although this study examined RF as a continuous variable, we tested the formulas examined in this analysis in the CARG toxicity calculator as a dichotomized variable using the same cutoff. The AUC of the ROC of the CARG toxicity score remains consistent no matter which CrCl formula is utilized.

These findings are relevant to clinical practice because the worldwide population is aging and there is an association between cancer and aging and between aging and decline in RF. Although not all older adults experience a change in RF with aging, in general there is a steady decline in RF of 0.75–1.0 mL/minute/year beginning at age 50 [26, 27]. These individuals are at increased risk for CRT and tools are needed to better define their risk in order to aid in ideal treatment planning.

Supporting our data to use ABW in RF calculations is a recent study which found CrCl by CG using ABW more comparable to measured GFR in older patients (>70 years old) than normalized body weight [33]. A notable exception is extremely obese patients for whom AjBW has typically been recommended for CrCl calculations [17, 25]. As a weight based formula, CG has been shown to overestimate CrCl in higher body weight and edematous individuals [34]. Hence, one hypothesis is that the correlation between Grade 3–5 toxicities and CG with ABW is due to an overestimation of the obese patient's RF and higher chemotherapy dose. However, the exact proportion of patients in whom CG with ABW was actually used to calculate the chemotherapy dose is not known and overall obese patients constituted <25% of all patients in our cohort which is considerably lower than in the

general US population. Additionally, although they did not meet statistical significance, the OR for CG, Jelliffe and Wright using adjusted and IBW were all over 1.0, supporting the association between decreased RF and increased CRT. If the association between CG with ABW and CRT were due to overestimation of RF in obese patients, we would not expect the OR for the formulas using adjusted and IBWs to be similar to the OR for the formulas using ABW.

The results of this study show that the association between decreased RF and increased odds of CRT is present regardless of whether patients receive medications which require dose adjustment for renal function or not. These results are therefore applicable to all patients regardless of the chemotherapy regimen they receive. A recent study presented at the 2014 American Society of Clinical Oncology meeting found that among older women with breast cancer treated with doxorubicin (which does not require dose reduction in renal impairment) and cyclophosphamide (which only requires dose reduction when CrCl is $<10\text{mL/min}$ [35]), those with renal impairment were more likely to develop chemotherapy toxicity than those with better RF [36]. This indicates that the relationship between decreased RF and increased CRT is not entirely dependent upon the renal metabolism of the drug. These data support our findings and suggest that decreased RF may be a surrogate for decreased physiologic reserve.

This study has limitations. This is a retrospective analysis, and validation in a larger cohort with results stratified by tumor type may provide additional clinical utility, as would studies addressing how various interventions (dose reductions, schedule alterations, etc.) can mitigate this increased risk. Furthermore, we did not have data regarding whether patients had their first cycle chemotherapy doses adjusted based on RF (i.e., a primary dose reduction). However, very few patients ($N=14$) who had a primary dose reduction reported kidney or liver disease as a comorbidity and there were no significant differences in toxicity rates between patients who had a primary dose reduction and those who did not [37]. Only 4% of the population was over the age of 85, only 2% had $\text{BMI}<18$, and only 4% had a $\text{BMI}>35$. These small numbers limit our ability to apply these results to these specific populations. Grade 3–5 toxicities were captured in this study, but certain grade 2 toxicities can have important clinical implications in this population.

We examined 4 commonly used formulas in this study, however, other formulas exist, such as the CKD-EPI formula. CKD-EPI is thought to be more accurate than MDRD for estimating GFR. This formula however, was not available at the time of the analysis, and CKD-EPI study population included only a small percentage of patients (13%) over the age of 65, and no patients over the age of 75, and therefore maybe less applicable to our study [38, 39]. However, it warrants inclusion in future studies that assess RF and CRT risk.

Furthermore, between 2007–2011, clinical laboratories across the United States updated their creatinine assays (calibrated to isotope dilution mass spectrometry [IDMS]) in compliance with creatinine standardization recommendations in order to produce more accurate RF estimates [40]. An updated MDRD equation was created and widely utilized to reflect this change [41]. As some patient creatinine values were obtained before this change was implemented, all GFR calculations were performed utilizing the original MDRD

formula, which may have led to less precise GFR estimations. However, despite the fact that this study was conducted amidst the IDMS conversion, in general IDMS sCr values (due to the presence of non-creatinine chromogens) are somewhat lower than nonstandardized creatinine values. The influence of these substances is more significant at the lower sCr levels as their proportion does not change as sCr goes up. We therefore hypothesize that the relationship between decreased CrCl and increased toxicity holds despite the study being conducted in the midst of the IDMS conversion. Nephrologists have highlighted the importance of considering body surface area when calculating RF and therefore express RF in terms of mL/min/1.73 meters squared. Although oncologists have not yet adopted this approach they do account for possible RF estimation errors attributed to body weight, by utilizing adjusted and IBW which was evaluated in this study. Further education regarding the utility of expressing RF in terms of mL/min/1.73 meters squared in oncology practice is needed.

Despite these limitations, these results reinforce the importance of estimating RF in older adults with cancer prior to initiation of a new chemotherapy regimen to assess for risk of CRT and confirm that sCr alone is not an adequate assessment of renal function.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Patient Characteristics (N=492)

Characteristics	Number	Percentage
Age, years		
65–69	171	35
70–74	125	25
75–79	105	21
80–84	71	14
85–91	20	4
Sex		
Female	276	56
Male	216	44
Cancer type		
Breast	56	11
Lung	139	28
GI	133	27
GYN	87	18
GU	50	10
Other	27	6
Cancer stage		
I	23	5
II	58	12
III	108	22
Limited	2	0
IV/extensive	301	61
Education levels		
Less than high school	17	3
High school	172	35
Associate/bachelor's	199	40
Advanced degree	103	21
Missing	1	0
Marital status		
Married	299	61
Widowed	113	23
Single	16	3
Separated, divorce	64	13
Employment status		
Full or part time	83	17
Retired, homemaker, unemployed	387	79

Characteristics	Number	Percentage
Disabled, medical leave	21	4
Missing	1	0
Household composition		
Live alone	105	21
Live with spouse, partner, or child	383	78
Missing	3	0
Race/ethnicity		
White	420	85
Black	41	8
Asian	25	5
Other	6	1

Table 2

Mean CrCl (Jelliffe, Cockcroft Gault and Wright) and Mean GFR (MDRD) for actual, ideal, and adjusted body weight (BW) calculations

Formula	Actual BW		Ideal BW		Adjusted BW	
	Mean (SD)	Median (Range)	Mean (SD)	Median (Range)	Mean (SD)	Median (Range)
Jelliffe	61.86 (20.23)	59.39 (16.47– 147.37)	56.78 (18.25)	54.89 (15.97– 119.41)	59.57 (19.02)	57.18 (16.47– 128.67)
Cockcroft	71.83 (26.57)	68.46 (18.47– 209.32)	56.91 (20.37)	54.55 (17.62– 132.11)	63.70 (22.62)	60.74 (18.47– 138.10)
Wright	78.03 (24.96)	74.76 (21.47– 175.09)	71.71 (22.86)	69.87 (20.82– 148.39)	75.21 (23.70)	72.34 (21.47– 152.87)
MDRD	78.76 (24.73)	76.51 (16.33– 171.37)				

Table 3

Percentage of patients with normal and compromised renal function

	Renal Function (mL/min)			
	<30	30–59	60–89	≥90
	N (%)	N (%)	N (%)	N (%)
Jelliffe actual BW	28 (5.7%)	227 (46.1%)	189 (38.4%)	48 (9.8%)
Jelliffe ideal BW	34 (6.9%)	271 (55.1%)	162 (32.9%)	25 (5.1%)
Jelliffe adjusted BW	32 (6.5%)	244 (49.6%)	184 (37.4%)	32 (6.5%)
Cockcroft actual BW	22 (4.5%)	149 (30.3%)	217 (44.1%)	104 (21.1%)
Cockcroft ideal BW	43 (8.7%)	256 (52%)	159 (32.3%)	34 (6.9%)
Cockcroft adjusted BW	29 (5.9%)	213 (43.3%)	189 (38.4%)	61 (12.4%)
Wright actual BW	14 (2.8%)	114 (23.2%)	221 (44.9%)	143 (29.1%)
Wright ideal BW	14 (2.8%)	158 (32.1%)	228 (46.3%)	92 (18.7%)
Wright adjusted BW	14 (2.8%)	127 (25.8%)	227 (46.1%)	124 (25.2%)
MDRD	12 (2.4%)	111 (22.6%)	247 (50.2%)	122 (24.8%)

Association between 10 mL/min decrease in renal function and odds of chemotherapy toxicity for actual, ideal, and adjusted body weight (BW) calculations, for all chemotherapy types

Table 4

Formula	Actual BW		Ideal BW		Adjusted BW	
	OR* (95% CI)	P value	OR* (95% CI)	P value	OR* (95%CI)	P value
Jelliffe	1.09 (1.00–1.19)	0.061	1.06 (0.96–1.17)	0.264	1.08 (0.98–1.18)	0.125
Cockcroft	1.12 (1.04–1.20)	0.002	1.04 (0.96–1.14)	0.330	1.07 (0.99–1.16)	0.086
Wright	1.06 (0.99–1.14)	0.091	1.04 (0.96–1.12)	0.366	1.05 (0.98–1.14)	0.183
MDRD	1.02 (0.95–1.10)	0.504				

* ORs per 10 ML/min decrease in CrCl/GFR are derived from unconditional logistic regression.

Association between renal function and odds of chemotherapy toxicity: comparing the lowest 10 percentile to the rest

Table 5

Formula	Actual BW OR* (95% CI)	P value	Ideal BW OR* (95% CI)	P value	Adjusted BW OR* (95% CI)	P value
Jelliffe	2.12 (1.12–4.02)	0.021	2.97 (1.51–5.86)	0.002	2.97 (1.51–5.86)	0.002
Cockcroft	1.73 (0.93–3.21)	0.084	2.12 (1.12–4.02)	0.021	2.64 (1.36–5.13)	0.004
Wright	2.12 (1.12–4.02)	0.021	2.12 (1.12–4.02)	0.021	2.97 (1.51–5.86)	0.002
MDRD	2.12 (1.12–4.02)	0.021				

* ORs comparing patients in the lowest 10 percentile of CrCl/GFR to the rest are derived from unconditional logistic regression.