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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.
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.

1. 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

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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 AjBW 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.

2. 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.

2.1. Study Schema

Prior to starting chemotherapy, patients completed an assessment that included geriatric assessment (GA) variables and sociodemographics. 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.

2.2. 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 m 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 kg + (2.3 kg × (height in inches − 60)) for male and 45.5 kg + (2.3 kg × (height in inches − 60) for female; AjBW was calculated as 0.3 × (actual body weight − ideal body weight) + 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).

3. Results

3.1. 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.

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