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A Comparison of Measured Creatinine Clearance versus Calculated Glomerular Filtration Rate for Assessment of Renal Function before Autologous and Allogeneic BMT

Theresa Hahn, Song Yao, Lauren M. Dunford, Julie Thomas, James Lohr, Pradeep Arora, Minoo Battiwalla, Shannon L. Smiley, Philip L. McCarthy, Jr.

Common blood and marrow transplantation (BMT) eligibility criteria include a minimum glomerular filtration rate (GFR) that may vary by regimen intensity. GFR is often estimated by measurement of creatinine clearance in a 24-hour urine collection (24-hr CrCl), an inconvenient and error-prone method that overestimates GFR. The study objectives were to determine which of 6 GFR calculations: Cockroft-Gault (CG), modified CG (mCG), Modification of Diet in Renal Disease I (MDRD1), MDRD2, Jelliffe, and Wright, consistently underestimated measured 24-hr CrCl pre-BMT. We retrospectively analyzed 98 consecutive allogeneic (n = 48) or autologous (n = 50) adult BMT patients from January 2006 to April 2007. All 6 formulas were significantly ($P < .001$) correlated with 24-hr CrCl with $R = 0.64$ (Wright), 0.63 (CG), 0.61 (mCG), 0.61 (Jelliffe), 0.54 (MDRD2), and 0.50 (MDRD1). When compared to the measured 24-hr CrCl, MDRD2 consistently underestimated it in the highest proportion of patients (66%, $P < .001$), compared with MDRD1 (65%, $P < .001$), Jelliffe (61%, P = NS), mCG (55%, P = NS), Wright (34%, $P < .001$), and CG (34%, $P = .001$). Measured 24-hr CrCl, pre-BMT serum Cr, and all 6 equations were not predictive of renal regimen-related toxicity (RRT) post-BMT. The Wright and CG formulas are closest to, but overestimate 24-hr CrCl in 66% of patients. In comparison, MDRD2 consistently underestimates 24-hr CrCl in 66%. Although MDRD2 is the most conservative formula, all 6 formulas gave reasonable estimates of GFR and any of the 6 equations can replace the measured 24-hr CrCl. Larger analyses and transplantation of patients with GFR <50 mL/min may better define subgroups at risk for renal RRT.

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INTRODUCTION

Patients undergoing blood and marrow transplantation (BMT) are at risk for several toxicities, including renal regimen-related toxicity (RRT), because of their exposure to high-dose chemotherapy agents and total body irradiation (TBI) [1-4]. Assessment of organ status (including kidney, liver, pulmonary, and cardiac function) prior to BMT is usually required; however, eligibility criteria vary between centers. Creatinine clearance measured in a 24-hour urine collection (24-hr CrCl) is an inexpensive, but error-prone and inconvenient method for assessing renal function. Glomerular filtration rate (GFR) cannot be measured directly, but can be estimated using urinary clearance of molecular isotopes such as ^{99m}Tc-DTPA, ^{125}I-iothalamate, or ^{51}Cr-EDTA, which are investigational, costly, and not widely available, plasma clearance of contrast agents such as isohexol that cannot be used in patients with an iodine allergy, or urinary clearance of the polysaccharide inulin, which requires precisely timed measures of blood and urine [5-8].

There are several validated equations using different parameters to estimate GFR, offering a very cost-effective and rapid method to evaluate renal function. One study has evaluated several prediction models in pediatric BMT patients [9]; however, there are no publications evaluating GFR equations in adult BMT patients. The appropriateness of several GFR equations has been examined in oncology patients with varying results [8,10-12]. In elderly (≥70 years) cancer

From the Blood and Marrow Transplantation Program, Department of Medicine, Roswell Park Cancer Institute, Buffalo, New York.
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Correspondence and reprint requests: Theresa Hahn, PhD, Department of Medicine, Roswell Park Cancer Institute, Elm & Carlton Streets, Buffalo, NY 14263 (e-mail: Theresa.hahn@roswellpark.org).
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patients with a GFR >50 mL/min, the Wright formula was reported as the most accurate and least biased calculation of GFR, compared to the more commonly used Cockroft-Gault (CG) and Jelliffe formulas [10]. The Jelliffe formula produced the greatest positive bias (overestimation) when used to estimate carboplatin clearance in gynecologic cancer patients [11]. A study of bladder cancer patients treated on clinical trials demonstrated low concordance between measured 24-hr CrCl and calculated CrCl using 12 equations. There was a poor correlation between the calculated CrCl and the ability to complete 3 cycles of cisplatin-based chemotherapy, and the authors concluded that most formulas for renal function underestimated the measured 24-hr CrCl [13].

The following 6 equations are most often examined in the oncology literature: CG, modified CG (mCG), Modification of Diet in Renal Disease 1 (MDRD1), MDRD2, Jelliffe, and Wright [14-17]. Currently, there are no recommendations or published studies delineating the most appropriate GFR prediction equation for screening pretransplant kidney function in the adult BMT population. Our study objectives were to (1) determine which of 6 GFR calculations could be utilized as an estimate for renal function prior to BMT in place of the 24-hr CrCl, and (2) determine if the GFR predicted by any of the equations is associated with subsequent development of moderate to severe renal RRT.

METHODS

Patients

We performed a retrospective analysis of 98 consecutive adult (≥18 years) patients who underwent allogeneic (n = 48) or autologous (n = 50) BMT from January 2006 and April 2007 at Roswell Park Cancer Institute (RPCI). Allogeneic BMT patients received myeloablative conditioning regimens, unless they had compromised physical functioning, organ dysfunction, older age, or had a prior autologous or allogeneic BMT. The minimum 24-hr CrCl was 50 mL/min for myeloablative and 40 mL/min for reduced-intensity conditioning (RIC) regimens. Patients who underwent BMT with a 24-hr CrCl <40 mL/min received an autologous BMT with a reduced melphalan (Mel) dose (100-120 mg/m^2). This study was reviewed and approved by the institutional review board at RPCI. All data have been deidentified.

Data Collection

All patients had 24-hr CrCl performed as part of their routine pre-BMT evaluation. Patient compliance with 24-hr CrCl collection was assessed by direct patient questioning, comparison with prior 24-hr CrCl collections, comparison to the normal expected creatinine excretion rate, and clinical judgment. Serum Cr and albumin were obtained as part of a routine metabolic profile, drawn within 0-3 days of the 24-hr CrCl collection. Urine collection was completed for all patients within 30 days pre-BMT, and for most patients within 2 weeks pre-BMT. Patient height and weight were measured in the RPCI BMT clinic 1-2 days prior to the initiation of the transplant regimen. Age, ethnicity, and sex were collected from hospital demographic data. The following standard formula was used to calculate 24-hr CrCl: $(Cr_{urine} \times V_{urine})/(Cr_{serum} \times 1440$ min) [5]. All urine and serum testing was performed in a single RPCI lab. In addition, GFR was calculated retrospectively for each patient using 6 equations: CG, mCG, MDRD1, MDRD2, Jelliffe, and Wright (see Table 1) [14-17].

Renal RRT

Renal RRT was defined according to standard published criteria as follows: grade 0 = no increase from baseline serum Cr; grade 1 = any increase over baseline serum Cr; grade 2 = doubling of baseline serum Cr; grade 3 = requirement of dialysis; and grade 4 = death from renal failure [18]. Renal RRT using

Table 1. Models for Estimating Glomerular Filtration Rate (GFR) in Adults

24-hr CrCl (mL/min)	$\frac{Cr_{urine} * V_{urine}}{Cr * 1440}$
Cockroft-Gault (mL/min)	$\frac{(140-age) * weight * (1-0.15 * sex)}{72 * Cr}$
Modified Cockroft-Gault (mL/min/1.73m^2)	$\frac{(140-age) * weight * (1-0.15 * sex)}{72 * Cr} * \frac{1.73}{BSA}$
MDRD1 (mL/min/1.73m^2)	$170 * Cr^{-0.999} * age^{-0.176} * BUN^{-0.017} * alb^{0.318} * (1-0.238 * sex) * (1 + 0.18 * race)$
MDRD2 (mL/min/1.73m^2)	$(186 * Cr^{-1.154} * age^{-0.203}) * (1-0.258 * sex) * (1 + 0.212 * race)$
Jelliffe (mL/min/1.73m^2)	$\frac{[98-0.8 * (age-20)] * BSA * (1-0.1 * sex)}{1.73 * Cr}$
Wright (mL/min)	$\frac{(6580-38.8 * age) * BSA * (1-0.168 * sex) * 0.0113}{Cr}$

age indicates years; weight, kg; sex, male = 0, female = 1; Cr, serum creatinine, mg/dL; V, volume, mL; alb, serum albumin; BUN, blood urea nitrogen; BSA = $\sqrt{(\text{height in cm} * \text{weight in kg})/3600}$; race, Caucasian = 0, other ethnicity = 1.