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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

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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 1 (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

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.

this toxicity scale was documented for each patient on a weekly basis from the start of conditioning regimen to day +100 post-BMT.

Statistical Analysis

Scatter plots with regression lines and boxplots were constructed for visualization. Outlier patient data was quality checked by 2 authors independently. The Pearson correlation coefficient was used for linear regression to compare the overall precision of calculated GFR for each of 6 equations versus measured 24-hr CrCl. The *P*-values for *R* tested the null hypothesis that the slope of the regression line = zero, that is, that the relationship between measured CrCl and predicted GFR is random and unpredictable. Wilcoxon signed rank test was used to examine the ability of each prediction equation to underestimate GFR, a measure of negative bias. Univariate analyses used logistic regression with the dichotomous outcome: RRT grade 2-4 versus RRT grade 0-1. All *P* values were 2 sided, with $P < .05$ considered statistically significant. Multivariate analyses could not be performed because of colinearity of the prediction equations with the covariates. Subgroup stratification by autologous versus allogeneic BMT and myeloma versus nonmyeloma diagnosis was performed. All statistical analyses were performed using SPSS 16.0 (SPSS, Inc., Chicago, IL).

RESULTS

Comparison of Measured Creatinine Clearance and Calculated GFR

Patient characteristics are shown in Table 2. We compared the measured 24-hr CrCl for each patient with GFR predicted by each of the 6 formulas using linear regression. All 6 formulas were significantly ($P < .0001$) correlated with measured 24-hr CrCl with correlation coefficients (*R*) of 0.64 (Wright), 0.63 (CG), 0.61 (mCG), 0.61 (Jeliffe), 0.54 (MDRD2), and 0.50 (MDRD1) (see Figure 1). Because the measured 24-hr CrCl overestimates the true GFR [19], we also examined the degree to which each prediction equation underestimated the measured 24-hr CrCl. MDRD2 consistently underestimated GFR in the highest proportion of patients (66%, $P < .001$), compared to MDRD1 (65%, $P = .001$), Jelliffe (61%, $P = $ NS), mCG (55%, $P = $ NS), Wright (34%, $P < .001$) and CG (34%, $P = .001$) (see Table 3). Underestimation of the measured 24-hr CrCl would likely be most critical at the lowest range (40-70 mL/min), where MDRD2 performed best (44% underestimation), followed by mCG (31%), Jeliffe (31%), MDRD1 (31%), CG (19%), and Wright (6%).

Table 2. Patient Characteristics (n = 98)

Patient Variables	N
Sex	
F	48
M	50
Median (Range) age in years	48 (20-74)
Race	
Caucasian	91
Other	7
Donor relation	
Autologous	50
Related	17
Unrelated	31
Conditioning regimen	
Myeloablative	57
Reduced Intensity	26
Nonmyeloablative	15
Conditioning regimen	
Total body irradiation-based	8
No total body irradiation	90
Stem cell source	
Bone marrow	12
Peripheral blood	86
Prior BMT	
No	72
Yes	26
Disease	
Acute leukemia	26
Hematologic disorder	8
Lymphoma	44
Myeloma/amyloidosis	16
Solid tumor	4
Median (Range) KPS at BMT	80 (50-90)
Median (Range) weight in kg	84.2 (47.9-149.8)
Median (Range) BSA	2.01 (1.48-2.76)
Median (Range) serum creatinine	0.9 (0.4-2.2)
Median (Range) albumin	4 (2-4.9)
Median (Range) blood urea nitrogen	15 (2-36)
Median (Range) measured 24hr CrCl	99.5 (36.5-288)
Median (Range) Calculated GFR—CG	107.7 (40-337)
Median (Range) Calculated GFR—ModCG	95.5 (42-262)
Median (Range) Calculated GFR—MDRD1	85.0 (37-287)
Median (Range) Calculated GFR—MDRD2	87.4 (34-283)
Median (Range) Calculated GFR—Jelliffe	92.3 (38-271)
Median (Range) Calculated GFR—Wright	109.1 (46-315)

Figure 2 depicts the percent difference between each of the 6 formulas and the measured 24-hr CrCl at different levels of measured 24-hr CrCl (40-70, 70-90, 90-120, and 120+ mL/min) for each of the 6 formulas. Positive values above the horizontal line indicate the calculated formula overestimated the measured 24-hr CrCl; negative values indicate underestimation. The CG model overestimated measured 24-hr CrCl at all GFR levels, whereas the MDRD2 demonstrated the least overestimation, especially at the lower end of the GFR range (40-70 and 70-90 mL/min). The MDRD2, MDRD1, Jelliffe, and mCG formulas were less likely to overestimate 24-hr CrCl when compared to the CG or Wright formulas. Therefore, MDRD2, MDRD1, Jelliffe, and mCG are recommended as the best formulas for underestimation of GFR, especially near the transplant eligibility threshold.
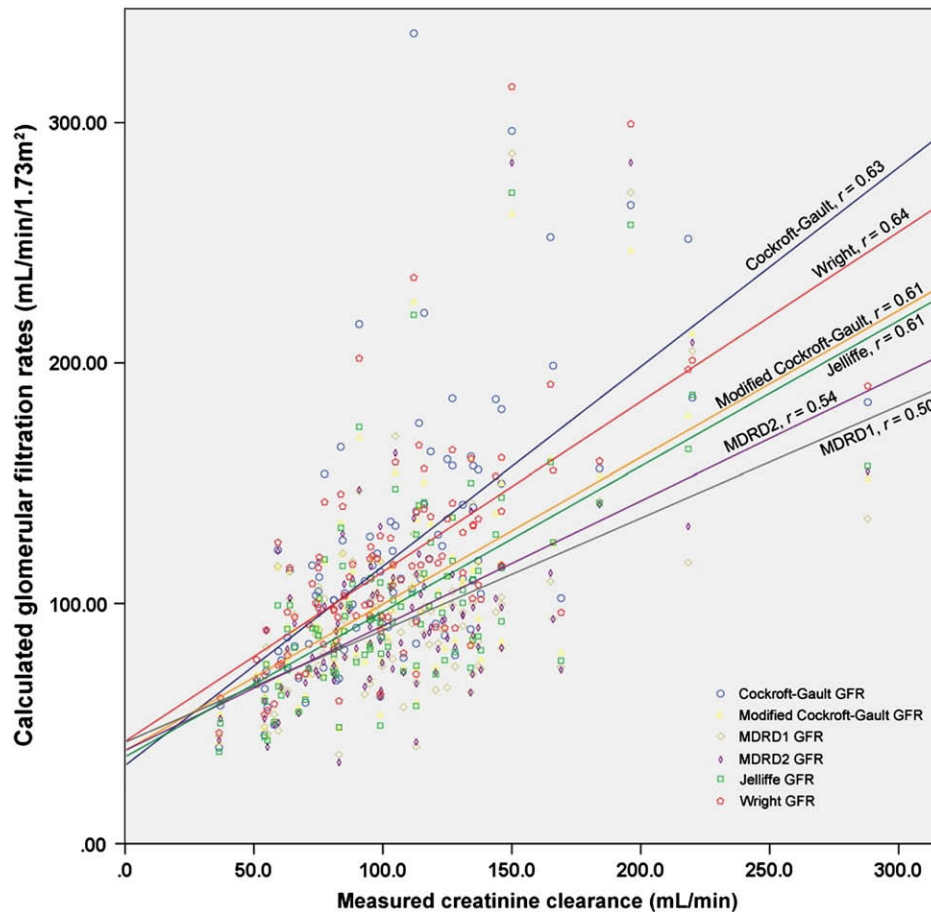
Figure 1. Scatterplots and fitted regression lines for measured creatinine clearance versus calculated glomerular filtration rate for 6 models.

Assessment of validity

Four patients were consistent outliers in 4 or more formulas (Patient IDs 39, 60, 92, and 97); however, they were not excluded from any analyses. Their calculated formulas far exceeded their measured 24-hr CrCl, and may represent patient errors in the 24-hr CrCl collection. However, 47% of females and 80% of males were below the normal creatinine excretion rates of 15-20 mg/kg/24 hours and 20-25 mg/kg/24 hours, respectively, based on the measured 24-hr CrCl collection. Surprisingly, the patients at the extreme ends of the creatinine excretion rates were not the discordant outliers in Figure 2. Because most BMT patients have received prior cytotoxic therapy, the low creatinine excretion rates may represent deconditioning and lost muscle mass during previous therapy.

Incidence and Risk Factors for Renal RRT

The incidence of renal RRT was 24%, 57%, 18%, 1%, and 0% for grades 0, 1, 2, 3, and 4, respectively. Measured 24-hr CrCl, serum Cr, and all 6 GFR calculations were not predictive of renal RRT post-BMT. Significant univariate predictors of grades 2-3 renal RRT were: allogeneic BMT, RIC/nonmyeloablative regimens, Karnofsky Performance Score (KPS) ≤80

and pre-BMT albumin ≤3.7 g/dL. In allogeneic BMT patients, BMI >35, KPS ≤80, and albumin ≤3.8 g/dL were significantly associated with grades 2-3 renal RRT, whereas in autologous BMT patients, baseline serum Cr ≥1.1 was the only significant factor. As noted in the Methods section, multivariate analyses could not be performed because of colinearity of the prediction equations with the covariates.

Interestingly, patients who received RIC or non-myeloablative conditioning had an increased risk of grade 2-3 renal RRT. Compared to myeloablative regimens, patients who received RIC or nonmyeloablative conditioning were more likely to be treated for acute leukemia or a hematologic disorder (54% versus 24%, $P = .0009$), have a lower KPS (41% versus 15% with KPS <80, $P = .003$), have an unrelated allogeneic donor (66% versus 7%, $P < .0001$), and have a prior BMT (54% versus 7%, $P < .0001$). Therefore, patients who received these lower intensity regimens had characteristics related to increased risk of renal toxicity.

DISCUSSION

The Cockroft-Gault formula is the most commonly studied equation, and was originally developed

Table 3. Difference between Measured Creatinine Clearance and Calculated Glomerular Filtration Rate

		Measured Creatinine Clearance (mL/min)				
		40-70 (n = 16)	70-90 (n = 21)	90-120 (n = 31)	120+ (n = 30)	Total (n = 98)
CG	median (range) % difference[1]	21.9 (−16.4∼106.2)	22.3 (−17.2∼98.8)	14.4 (−38.1∼201.0)	3.2 (−39.5∼97.7)	14.0 (−39.5∼201.0)
	% underestimation[2]	19%**	29%**	35%*	43%	34%***
mCG	median (range) % difference[1]	14.0 (−19.8∼93.5)	15.2 (−42.5∼59.6)	−3.9 (−48.2∼101.1)	−17.2 (−53.0∼74.5)	−4.0 (−53.0∼101.1)
	% underestimation[2]	31%*	29%*	55%	87%***	55%
MDRD1	median (range) % difference[1]	9.6 (−20.9∼94.7)	3.8 (−55.3∼43.1)	−17.7 (−64.2∼61.6)	−33.4 (−56.5∼91.4)	−14.8 (−64.2∼94.7)
	% underestimation[2]	31%*	38%	74%**	93%***	65%**
MDRD2	median (range) % difference[1]	8.3 (−27.2∼105.5)	7.0 (−59.2∼56.2)	−12.3 (−62.5∼62.2)	−32.2 (−57.2∼88.9)	−12.0 (−62.5∼105.5)
	% underestimation[2]	44%	43%	68%*	93%***	66%**
Jelliffe	median (range) % difference[1]	9.8 (−22.1∼67.3)	11.1 (−41.6∼57.1)	−6.3 (−50.4∼96.4)	−21.6 (−54.9∼80.5)	−7.1 (−54.9∼96.4)
	% underestimation[2]	31%	33%*	68%	90%***	61%
Wright	median (range) % difference[1]	25.6 (−0.8∼111.4)	27.6 (−28.4∼83.7)	6.8 (−37.5∼122.3)	−5.9 (−43.1∼110.0)	7.9 (−43.1∼122.3)
	% underestimation[2]	6%***	10%***	26%*	73%	34%***

CG indicates Cockroft-Gault model; mCG, modified Cockroft-Gault model; MDRD, Modification of Diet in Renal Disease.
* is <.05; ** is <.01; *** is <.001.
[1]Positive values indicate the calculated GFR is greater than the measured 24hr CrCl; negative values indicate the calculated GFR is less than the measured 24-hr CrCl.
[2]Asterisk denotes statistically significant difference from measured 24hr CrCl using Wilcoxon signed-rank test

to predict the 24-hr CrCl in a limited sample (<250) of Caucasian males [5,14]. The modified CG, Jelliffe, and Wright formulas were developed to account for body size and sex. The MDRD1 and MDRD2 formulas have the advantage of being developed to predict GFR measured by urinary clearance of ^{125}I-iothalamate in a large (>1000) sample of both males and females and European- and African-American participants. The MDRD2 formula has been validated in large and varied populations [5,6]. Therefore, the MDRD formula is recommended in adults by the

Kidney Disease Outcomes Quality Initiative (K/DO-QI^{TM}) guidelines of the National Kidney Foundation because it is the least biased and most accurate equation for GFR estimation [5].

However, the MDRD2 calculation is not as straightforward and easy to memorize as other formulas. Online resources exist in which the user is prompted to enter laboratory and demographic data necessary for the MDRD calculation and are then provided with the patient's GFR. There are several freely accessible Web sites (www.kdoqi.org or
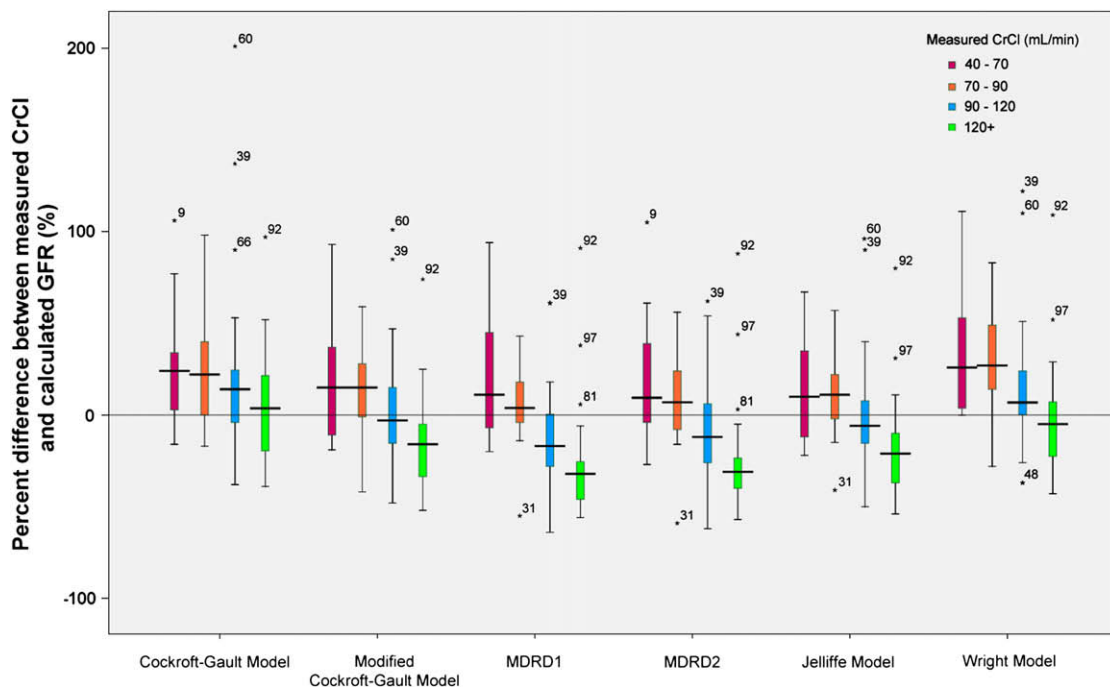

Figure 2. Boxplot of percent difference between measured creatinine clearance and calculated glomerular filtration rate at different ranges of measured creatinine clearance. Please note that the bar in color denotes the 25% to 75% percentile of percent difference, with median (50% percentile) as a short black line in the middle; error bars denote the range of percent difference; asterisks denote outliers with the patient ID.

http://www.nkdep.nih.gov/professionals/gfr_calcula-tors/index.htm) or the equation can be easily programmed or imported into calculators, PDAs, or laboratory systems.

We found no correlation between the pretransplant GFR estimation from any of the 6 equations or the measured CrCl and the development of posttransplant moderate to severe (grade 2-3) renal RRT. Because of the relatively low incidence of severe grade 3 renal toxicity (1%), a very large cohort would be necessary to examine a correlation with baseline GFR. Our results suggest a lower GFR threshold may be acceptable for BMT because of the relatively low incidence of severe renal toxicity observed. Larger analyses of patients undergoing BMT at a lower GFR threshold may better define subgroups at risk for renal RRT.

In our retrospective analysis, we identify MDRD2 as the most conservative equation for determining GFR as it most likely underestimates kidney function. However, the mCG, Jelliffe, and MDRD1 formulas also underestimate renal function and would be reasonable alternative calculations of 24-hr CrCl. The mCG and Jelliffe formulas require height and weight for BSA calculation in addition to the same laboratory and demographic data as the CG formula. MDRD1 requires additional laboratory data for blood urea nitrogen and albumin. Thus, we can recommend using the MDRD2, mCG, Jelliffe, and MDRD1 formulas for conservative estimates of renal function without the need to perform a 24-hr CrCl.

ACKNOWLEDGMENTS

REFERENCES

1. Zager RA. Acute renal failure in the setting of bone marrow transplantation. *Kidney Int*. 1994;46:1443-1458.
2. Gruss E, Bernis C, Tomas JF, et al. Acute renal failure in patients following bone marrow transplantation: prevalence, risk factors and outcome. *Am J Nephrol*. 1995;15:473-479.
3. Miralbell R, Bieri S, Mermillod B, et al. Chapuis B. Renal toxicity after allogeneic bone marrow transplantation: the combined effects of total-body irradiation and graft-versus-host disease. *J Clin Oncol*. 1996;14:579-585.
4. Foninck E, Cahn JY. Renal toxicity after bone marrow transplantation. *Int J Radiat Oncol Biol Phys*. 2004;58:661-662.
5. The Kidney Disease Outcome Quality Initiative. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis*. 2002;39 (2 Suppl. 1):S1-S246.
6. Peters AM. Quantification of renal haemodynamics with radionucleotides. *Eur J Nucl Med*. 1991;18:274-286.
7. Rehling M, Moller ML, Lund JO, et al. Simultaneous measurement of Tc-99mDTPA, Cr-51 EDTA and inulin in man. *Clin Sci*. 1984;66:613-619.
8. Holweger K, Bokemeyer C, Lipp HP. Accurate measurement of individual glomerular filtration rate in cancer patients: an ongoing challenge. *J Cancer Res Clin Oncol*. 2005;131: 559-567.
9. Jacobson P, West N, Hutchinson RJ. Predictive ability of creatinine clearance estimate models in pediatric bone marrow transplant patients. *Bone Marrow Transplant*. 1997;19: 481-485.
10. Marx GM, Blake GM, Galani E, et al. Evaluation of the Cockroft-Gault, Jelliffe and Wright formulae in estimating renal function in elderly cancer patients. *Ann Oncol*. 2004;15: 291-295.
11. Nagao S, Fujiwara K, Imafuku N, et al. Difference of carboplatin clearance estimated by the Cockroft-Gault, Jelliffe, Modified-Jelliffe, Wright or Chatelut formula. *Gyn Oncol*. 2005;99: 327-333.
12. Poole SG, Dooley MJ, Rischin D. A comparison of bedside renal function estimates and measured glomerular filtration rate (Tc^{99m}DTPA clearance) in cancer patients. *Ann Oncol*. 2002; 13:949-955.
13. Raj GV, Iasonos A, Herr H, Donat SM. Formulas calculating creatinine clearance are inadequate for determining eligibility for cisplatin-based chemotherapy in bladder cancer. *J Clin Oncol*. 2006;24:3095-3100.
14. Cockroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16:31-41.
15. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med*. 1999; 130:461-470.
16. Jelliffe RW. Creatinine clearance: bedside estimate. *Ann Intern Med*. 1973;79:604-605.
17. Wright JG, Boddy AV, Highley MS, et al. Estimation of glomerular filtration rate in cancer patients. *Br J Cancer*. 2001;84: 452-459.
18. Bearman SI, Appelbaum FR, Buckner CD, et al. Regimen-related toxicity in patients undergoing bone marrow transplantation. *J Clin Oncol*. 1988;6:1562-1568.
19. van Acker BA, Koomen GC, Koopman MG, et al. Creatinine clearance during cimetidine administration for measurement of glomerular filtration rate. *Lancet*. 1992;340: 1326-1329.