Effect of Renal Dysfunction on Toxicity in Three Decades of Cancer Therapy Evaluation Program–Sponsored Single-Agent Phase I Studies

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ABSTRACT

Purpose

Alterations in renal clearance of anticancer drugs can affect the occurrence of toxicities related to drug exposure. The National Cancer Institute and the US Food and Drug Administration (FDA) use different criteria to classify renal dysfunction. We examined those discrepancies and their potential association with the incidence of toxicities in patients enrolled onto Cancer Therapy Evaluation Program–sponsored single-agent phase I studies over three decades (1979 to 2010).

Methods

Data to estimate creatinine clearance according to the Cockcroft-Gault and Jelliffe formulas were available from 10,236 patients, and data to estimate creatinine clearance according to the six- and four-variable Modification of Diet in Renal Disease formulas were available from a subset ($n = 4,084$). Patients were classified according to National Cancer Institute and FDA criteria, and the rates of clinically relevant toxicities were evaluated within groups and compared among groups.

Results

Cockcroft-Gault estimated renal function improved over time, which may be attributed to an increase in weight of patients in the same time frame. Approximately 36% of patients enrolled onto phase I trials had mild renal dysfunction by FDA criteria. Relative to normal function, mild renal dysfunction was associated with a statistically significant but small increase in grade 3 or 4 non-hematologic toxicity and any relevant toxicities.

Conclusion

Patients with mild renal dysfunction by FDA criteria have routinely been enrolled onto phase I studies of antineoplastics without clinically meaningful increase in the risk of toxicity. In future oncology renal dysfunction trials based on the FDA classification, the FDA mild group may only need to be activated when the moderate and normal groups differ substantially in tolerability or pharmacokinetics.

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INTRODUCTION

Phase I studies of antineoplastics characterize toxicities and pharmacokinetic and pharmacodynamic properties, defining the maximum-tolerated dose (MTD), dose-limiting toxicities, and recommended phase II doses. Patients with renal dysfunction are often excluded because impaired renal function might be associated with increased toxicity, requiring dose adjustments to maintain safety.¹ Typical phase I eligibility has included a serum creatinine concentration (S_{Cr}) ≤ 1.5 mg/dL or an estimated creatinine clearance ($CrCl$) ≥ 60 mL/min. Pioneered by the Cancer and Leukemia Group B (CALGB)² and adopted

by the National Cancer Institute (NCI) Organ Dysfunction Working Group (ODWG), these criteria were the starting point for defining mild, moderate, and severe renal dysfunction groups based on intervals of 20 mL/min (Fig 1). The NCI/CALGB classification differs from generic guidance published by the US Food and Drug Administration (FDA), which defines severe, moderate, and mild renal dysfunction differently using unequal group intervals.³ Importantly, $CrCl \geq 60$ mL/min or $S_{Cr} \leq 1.5$ mg/dL is considered acceptable for oncology patients, which includes patients with mild renal dysfunction according to the FDA classification ($CrCl$, 50 to 79 mL/min). As a result, many patients enrolled onto

Fig 1. National Cancer Institute (NCI)/Cancer and Leukemia Group B (CALGB) and US Food and Drug Administration (FDA) categories of renal dysfunction and formulas used to estimate renal function. BSA, body-surface area; BUN, blood urea nitrogen; CrCl, creatinine clearance; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; S_{Cr} , serum creatinine concentration.

phase I studies of antineoplastic agents have mild renal dysfunction according to FDA criteria.

If mild renal dysfunction is not associated with a relevant increased risk of toxicity in phase I trials, future organ dysfunction trials of oncology agents may follow the FDA criteria and omit the mild renal dysfunction category from study designs. However, if mild renal dysfunction is associated with increased risk of toxicity in phase I trials, patients with mild renal dysfunction by FDA criteria might contribute disproportionately to setting the MTD and recommended phase II dose, leading to patients with normal renal function ($\text{CrCl} \geq 80 \text{ mL/min}$) potentially being underdosed.

To address the effects of classification systems on outcome, we analyzed the distribution of renal function and the association with hematologic and nonhematologic toxicity in patients enrolled onto Cancer Therapy Evaluation Program (CTEP) –sponsored phase I clinical studies according to the NCI/CALGB and FDA renal dysfunction criteria. In this study, we show that oncology organ dysfunction studies may be aligned with the FDA system and that renal dysfunction studies should be performed in those with moderate and worse renal dysfunction and only in patients with mild renal dysfunction if there is a difference between patients with moderate dysfunction and normal function.

METHODS

Data covered 10,236 patients in 373 CTEP-sponsored, single-agent phase I studies between 1979 and October 2010 in the Theradex database, involving 179 antineoplastic agents (Appendix Table A1, online only). The Theradex database is prospectively maintained by Theradex Systems (Princeton, NJ),

with robust data management and auditing practices. All NCI-sponsored clinical trials used for this analysis were reviewed and approved by the institutional review board where the study was conducted, and written informed consent was obtained from all patients. October 2010 was the cutoff date reflecting the recalibration of serum creatinine assays to an isotope dilution mass spectrometry traceable reference method across North America.⁴ Renal dysfunction trials were excluded. Records with age, sex, weight, creatinine, and date of first course were included. Children (age < 18 years) were excluded. The database included pretreatment information on each patient's serum albumin, blood urea nitrogen, and height and the agent used. Body-surface area (BSA) was calculated according to Mosteller.⁵ We estimated CrCl or glomerular filtration rate (GFR) with four formulas (Cockcroft-Gault [C-G], Jelliffe, six-variable Modification of Diet in Renal Disease [MDRD], and four-variable MDRD; Fig 1).⁶⁻⁹ CrCl data of 10,236 patients were estimated with C-G and Jelliffe formulas. Race was only available for patients after 1995 because collection of race data was prohibited by law before 1995. Therefore, only 4,084 patients had sufficient data to estimate CrCl and GFR with all formulas. On the basis of estimated CrCl and GFR, patients were sorted into NCI/CALGB and FDA renal function categories and 5-year periods.

Clinically relevant toxicities, defined as grade ≥ 4 hematologic toxicities and grade ≥ 3 nonhematologic toxicities in cycle 1 at least possibly related to study treatment, were extracted. To maximize the sensitivity to any relationship between toxicities and CrCl, only studies in which such toxicities occurred ($n = 282$) were included in the analyses. Next, only patients enrolled onto the top two dose levels of these trials were analyzed (dose levels at which dose-limiting toxicities most likely occurred and that eventually determined the MTD). The percentage of patients experiencing toxicity was tabulated by renal function classification. The association between CrCl (mild v normal) and toxicity was tested using the χ^2 test. Trends of toxicity with renal function were tested using the Cochran-Armitage test. Improved renal function over time was tested using the Jonckheere-Terpstra test. $P < .05$ was considered significant (without corrections for multiple testing).

Table 1. CrCl Distribution in CTEP Studies According to the Cockcroft-Gault and Jelliffe Formulas (N = 10,236)

Formula	NCI/CALGB Criteria (% of patients)				FDA Criteria (% of patients)			
	Severe: CrCl < 20*	Moderate: CrCl 20-39	Mild: CrCl 40-59	Normal: CrCl ≥ 60	Severe: CrCl < 30	Moderate: CrCl 30-49	Mild: CrCl 50-79	Normal: CrCl ≥ 80
Cockcroft-Gault	0.22	2.44	15.0	82.4	0.60	7.59	36.1	55.7
Jelliffe	0.24	3.77	27.8	68.2	0.68	14.0	52.8	32.7

Abbreviations: CALGB, Cancer and Leukemia Group B; CrCl, creatinine clearance; CTEP, Cancer Therapy Evaluation Program; FDA, US Food and Drug Administration; NCI, National Cancer Institute.

*CrCl in milliliters per minute for Cockcroft-Gault and milliliters per minute per 1.73 m² for Jelliffe.

RESULTS

Demographic Data

For the 10,236 patients, mean ($\pm$ standard deviation) age was 56.1 $\pm$ 12.7 years (range, 18 to 96 years; Appendix Table A2, online only), 58.7% were male (Appendix Table A3, online only), mean weight was 75.6 $\pm$ 18.5 kg (range, 25.3 to 233 kg; Appendix Table A4, online only), mean height (for patients with data and $\geq$ 100 cm) was 170.1 $\pm$ 10.3 cm (range, 100.5 to 203.0 cm; Appendix Table A5, online only), and mean BSA (for patients with data and $\geq$ 100 cm) was 1.88 $\pm$ 0.25 m² (range, 1.08 to 3.41 m²; Appendix Table A6, online only). After 1995, race was available for 4,118 patients; 88.4% were white, were 8.6% black or African American, 0.3% were native Hawaiian or other Pacific Islander, 2.5% were Asian, and 0.1% were American Indian or Alaskan native (Appendix Table A7, online only).

Renal Function Classification

The percentage of patients classified as having normal function or renal dysfunction varied by the formula used. The Jelliffe formula generated lower estimates of renal function than the more common C-G formula (Table 1; CrCl by C-G is assumed, unless indicated otherwise). Of the 10,236 patients, 82.4% had a CrCl $\geq$ 60 mL/min, having normal renal function by NCI/CALGB criteria. In contrast, only 55.7% of patients had normal renal function by FDA criteria (CrCl $\geq$ 80 mL/min). Of the patients with NCI/CALGB normal renal function (CrCl $\geq$ 60 mL/min), 32.4% (n = 2,729) had mild renal dysfunction by FDA criteria (CrCl 50 to 79 mL/min). Conversely, 73.9% (n = 2,729) of patients classified as having FDA mild renal dysfunction (CrCl 50 to 79 mL/min) had normal renal function (CrCl $\geq$ 60 mL/min) by NCI/CALGB criteria.

When all four formulas (C-G, Jelliffe, four-variable MDRD, and six-variable MDRD) were used to calculate CrCl and GFR for the 4,084 patients with race data (Table 2), the percentages of patients with NCI/CALGB normal (CrCl $\geq$ 60 mL/min) and FDA normal (CrCl $\geq$ 80 mL/min) renal function were similar to those calculated in the total group of 10,236 patients (Table 1). Depending on the formula used in the 4,084 patients, 32.1% to 49.6% of patients had FDA mild renal dysfunction. Appendix Figure A1 (online only) depicts the distribution of CrCl calculated by each of the four formulas.

Renal Function Over Time

Between 1979 and 2010, the proportion of patients with normal estimated renal function enrolled onto trials seemed to increase from 76% to 86% (Table 3, $P < .001$). Similar trends were observed using the FDA classification. The magnitude of this trend was smaller with CrCl by Jelliffe (Appendix Table A8, online only, $P < .001$).

Association of Toxicity With Calculated Renal Function

Eight thousand seven hundred sixty-five patients were enrolled onto trials with clinically relevant grade $\geq$ 4 hematologic or $\geq$ 3 nonhematologic toxicity (Appendix Table A9, online only). We further enriched for patients with these toxicities by selecting the subset of patients enrolled onto the top two dose levels, which are assumed to represent the MTD and the dose level above the MTD (Table 4). The percentage of patients experiencing grade 3 or 4 nonhematologic, grade 4 hematologic, or any clinically relevant toxicity seemed to trend down as estimated renal function improved (Fig 2). For example, grade 3 or 4 nonhematologic toxicity was observed in 37.5%, 33.8%, 28.6%, and 25.5% of patients with severe, moderate, and mild renal

Table 2. CrCl Distribution of Patients Enrolled After 1995 According to All Formulas (N = 4,084)

Formula	NCI/CALGB Criteria (% of patients)				FDA Criteria (% of patients)			
	Severe: CrCl < 20*	Moderate: CrCl 20-39	Mild: CrCl 40-59	Normal: CrCl ≥ 60	Severe: CrCl < 30	Moderate: CrCl 30-49	Mild: CrCl 50-79	Normal: CrCl ≥ 80
Cockcroft-Gault	0.12	1.37	12.2	86.3	0.29	5.36	32.1	62.2
Jelliffe	0.17	3.38	23.6	72.9	0.49	11.7	49.6	38.3
Six-variable MDRD	0.15	1.40	13.6	84.9	0.34	5.80	38.5	55.4
Four-variable MDRD	0.15	1.30	12.3	86.2	0.27	5.14	38.0	56.6

NOTE. Patients with missing blood urea nitrogen, albumin, or race were excluded.

Abbreviations: CALGB, Cancer and Leukemia Group B; CrCl, creatinine clearance; FDA, US Food and Drug Administration; MDRD, Modification of Diet in Renal Disease; NCI, National Cancer Institute.

*CrCl in milliliters per minute for Cockcroft-Gault formula and milliliters per minute per 1.73 m² for other formulas.

Table 3. Cockcroft-Gault–Calculated CrCl As a Function of Time

Year	NCI/CALGB Criteria					FDA Criteria				
	No. of Patients	% of Patients				No. of Patients	% of Patients			
		Severe: CrCl < 20 mL/min	Moderate: CrCl 20-39 mL/min	Mild: CrCl 40-59 mL/min	Normal: CrCl ≥ 60 mL/min		Severe: CrCl < 30 mL/min	Moderate: CrCl 30-49 mL/min	Mild: CrCl 50-79 mL/min	Normal: CrCl ≥ 80 mL/min
1979-1984	698	0.29	4.58	18.9	76.2	698	1.00	12.6	37.5	48.9
1985-1989	1,809	0.55	3.81	17.8	77.8	1,809	1.33	9.84	41.6	47.2
1990-1994	2,724	0.11	3.05	17.3	79.6	2,724	0.51	9.07	40.3	50.1
1995-1999	2,156	0.09	1.07	11.2	87.7	2,156	0.23	4.73	31.5	63.6
2000-2004	1,738	0.29	1.55	13.0	85.2	1,738	0.58	5.58	32.9	61.0
2005-2010	1,111	0.09	1.44	12.7	85.8	1,111	0.09	5.85	30.0	64.1
Trend over time, <i>P</i> *	< .001					< .001				

Abbreviations: CALGB, Cancer and Leukemia Group B; CrCl, creatinine clearance; FDA, US Food and Drug Administration; NCI, National Cancer Institute.

*Trend over time by Jonckheere-Terpstra test.

dysfunction and normal renal function, respectively, by FDA classification. Statistically significant differences between mild renal dysfunction and normal renal function were observed in frequencies of grade 3 or 4 nonhematologic toxicities and any clinically relevant toxicity (Table 4). The differences were larger when categorizing patients according to NCI/CALGB (current practice) relative to categorization according to the FDA system. Because only five of the 179 antineoplastic agents were kinase inhibitors (7-hydroxystaurosporine, flavopiridol, imatinib, orantinib, and pazopanib), these results are not likely biased by the emergence of tyrosine kinase inhibitors, and comparing tyrosine kinase inhibitors with other agents was not possible.

DISCUSSION

The likelihood of unintended adverse effects of pharmacotherapy increases with exposure. Patients with decreased metabolic and excretory organ function are likely to experience greater drug exposure. Therefore, phase I studies are conducted in patients with normal hepatic and renal function, followed by studies to define doses for

patients with decreased organ function. Such organ dysfunction trials are complex and require specific expertise in addition to multicenter collaborations as exemplified previously by CALGB and currently by the NCI-ODWG.

Cancer rates increase with age,¹⁰ and aging is associated with several physiologic changes, including decreased renal function estimated at 1 mL/min in GFR per year after age 40 years.¹¹⁻¹⁴ Consequently, patients with cancer often do not have normal renal function, but are characterized as having acceptable renal function. Specifically, CrCl ≥ 60 mL/min (or an S_{Cr} < 1.5 mg/dL) is the usual eligibility criterion for enrollment onto oncology phase I studies, which includes patients with mild renal dysfunction by FDA criteria. As a result, oncology organ dysfunction studies have classified patients as having mild, moderate, or severe renal dysfunction by CrCl ranges of 40 to 59, 20 to 39, and 0 to 19 mL/min, respectively. Patients on renal dialysis are often evaluated separately. These renal dysfunction groups were initially used in 1982 in studies of carboplatin¹⁵ and subsequently adopted by CALGB^{2,16-18} and the NCI-ODWG.¹⁹⁻²¹ In contrast, the FDA guidance classifies normal renal function as a CrCl ≥ 80 mL/

Table 4. Toxicity As a Function of Cockcroft-Gault CrCl

Toxicity	NCI/CALGB Criteria					FDA Criteria				
	% of Patients Experiencing Toxicities				<i>P</i> *	% of Patients Experiencing Toxicities				<i>P</i> *
	Severe: CrCl < 20 mL/min (n = 4)	Moderate: CrCl 20-39 mL/min (n = 472)	Mild: CrCl 40-59 mL/min (n = 472)	Normal: CrCl ≥ 60 mL/min (n = 2,850)		Severe: CrCl < 30 mL/min (n = 16)	Moderate: CrCl 30-49 mL/min (n = 228)	Mild: CrCl 50-79 mL/min (n = 1,157)	Normal: CrCl ≥ 80 mL/min (n = 1,997)	
Grade 3 nonhematologic	25.0	31.9	23.9	20.5		37.5	25.9	21.9	20.1	
Grade 4 nonhematologic	0.0	4.2	8.7	5.6		0.0	7.9	6.7	5.4	
Grade 3 or 4 nonhematologic	25.0	36.1	32.6	26.0	.003	37.5	33.8	28.6	25.5	.056
Grade 4 hematologic	25.0	19.4	14.0	12.8	.468	31.3	17.5	13.5	12.2	.304
Grade 5	0.0	1.4	1.1	0.6		0.0	1.8	0.9	0.4	
Any	50.0	51.4	40.5	34.4	.010	68.8	42.5	37.3	33.6	.036

NOTE. Denominator is number of patients enrolled onto top two dose levels of trials where any grade 4 hematologic, grade 3 or 4 nonhematologic, or grade 5 toxicities occurred. For nonhematologic toxicity, only the highest grade toxicity was counted for each patient. Every patient was counted once in each of the following three categories when listed separately: grade 3 or 4 nonhematologic, grade 4 hematologic, and grade 5 toxicity. For any toxicity, each patient was only counted once. A Cochran-Armitage trend analysis was performed comparing moderate versus mild versus normal. Significant one-sided *P* values (decreased toxicity for better renal function), not adjusted for multiple testing, were as follows: NCI/CALGB, grade 3 or 4 nonhematologic toxicity, *P* < .001; any toxicity, *P* < .001; FDA, grade 3 or 4 nonhematologic toxicity, *P* = .002; grade 4 hematologic toxicity, *P* = 0.021; any toxicity, *P* = .001.

Abbreviations: CALGB, Cancer and Leukemia Group B; CrCl, creatinine clearance; FDA, US Food and Drug Administration; NCI, National Cancer Institute.

*Mild v normal.

Fig 2. Frequency of different grades of toxicity as a function of the midpoint Cockcroft-Gault estimated creatinine clearance (CrCl) of the respective renal function group as classified according to the (A) National Cancer Institute (NCI)/Cancer and Leukemia Group B (CALGB) and (B) US Food and Drug Administration (FDA). heme, hematologic.

min, and mild, moderate, and severe renal dysfunction is classified as CrCl of 50 to 79, 30 to 49, and 0 to 29 mL/min, respectively.

Our data (Table 1) clearly demonstrate representation of patients (26.7%) with CrCl (C-G) between 60 and 79 mL/min in phase I studies of antineoplastic agents, classified as mild renal dysfunction according to guidelines defined by the FDA and the National Kidney Foundation.²² In the highest two dose levels of trials with toxicities, patients with FDA mild renal dysfunction were not much more likely to experience toxicity than those with FDA normal renal function (37.3% v 33.6%, respectively), even though statistical significance ($P = .036$) was observed (Table 4). This statistical significance despite small effect size is likely a reflection of the large sample size involved, and it should be noted that we did not correct for multiple testing. Our statistically significant, though minimal, effect is in line with Hyman et al,²³ who reported diminished CrCl as a predictor of toxicity ($P = .013$).

Classification according to NCI/CALGB criteria versus FDA criteria showed a larger difference in toxicity frequency between normal and mild groups (Table 4; eg, frequency of grade 3 or 4 nonhematologic toxicity in mild renal dysfunction v normal function was 32.6% v 26.0%, respectively, according to NCI/CALGB and 28.6% v 25.5%, respectively, according to FDA). This is attributable to the difference in toxicity rate in the patients with mild renal dysfunction as defined by the NCI/CALGB versus the FDA. This suggests that patients with an estimated CrCl between 40 and 49 mL/min (included in NCI/CALGB mild renal dysfunction category but the FDA moderate category) are primarily responsible for the differences in frequency of toxicity between the NCI/CALGB mild and normal groups.

Given the small difference in toxicity between patients with FDA mild dysfunction and normal renal function, going forward, studies of antineoplastic agents in patients with renal dysfunction need not include the group of patients with FDA mild dysfunction. Rather, we believe the data argue for enrollment of patients into moderate (CrCl 30 to 49 mL/min), severe (CrCl < 30 mL/min), and dialysis renal dysfunction groups, anchored with a normal (CrCl $\geq$ 80 mL/min) group. Only when the moderate group results in an MTD or pharmacokinetics that are different from those of the normal group would

enrollment onto a mild (CrCl 50 to 79 mL/min) renal dysfunction group be warranted.

Applying the FDA categorization and eliminating the mild group, conditional on the MTD in the normal and moderate groups, would have a number of advantages. It would resolve disparities in clinical trial design between oncology and other therapeutic areas. It would simplify the logistics of renal dysfunction studies by decreasing the number of classifications. Finally, the current CALGB and NCI criteria for severe renal dysfunction are problematic because most patients with C-G CrCl less than 10 mL/min are on dialysis. Few patients meet the definition of severe renal dysfunction not on dialysis, and in previous oncology renal dysfunction studies, accrual goals for this group have rarely been fulfilled.

An unintended consequence of this novel approach would be potential discrepancies between the MTD established in the initial phase I study (CrCl $\geq$ 60 mL/min) and the true MTD in the normal group (CrCl $\geq$ 80 mL/min) of the organ dysfunction trial, particularly with an agent that is predominantly renally cleared. Current renal dysfunction trial designs do not escalate above the phase I MTD of an agent. However, if FDA mild and normal groups in the organ dysfunction trial have the same MTD (with dose escalation capped at the phase I MTD), there are two possible interpretations. Either there is no effect of mild versus normal renal function on tolerability or the normal group has a higher true MTD than the phase I MTD. Assuming tolerability is exposure driven, pharmacokinetic studies are crucial to provide better understanding of these issues and could prompt further dose escalation in the normal group to an MTD above that of previous studies. The difference between what is considered normal by the FDA and acceptable by the oncology community will only be exacerbated if the FDA adopts their intended changes in how they define renal groups. A draft guidance has been developed, and the intended reclassification would define mild dysfunction as CrCl of 60 to 89 mL/min (currently 60 to 79 mL/min) and normal function as CrCl $\geq$ 90 mL/min (currently $\geq$ 80 mL/min).²⁴ This reclassification would diminish further any effects we observed between the FDA mild and normal groups (data not shown). Abandoning the commonly used oncology phase I eligibility criterion of CrCl $\geq$ 60

mL/min (or $S_{Cr} < 1.5$ mg/dL) and limiting enrollment to patients with better renal function would severely reduce enrollment in this inherently older population.

Our analysis also indicates that the percentage of patients with mild renal dysfunction has decreased between 1979 and 2010 (Table 3), with a sharp decrease between 1990 to 1994 and 1995 to 1999. Although superficially this would suggest that the kidney function of patients enrolled onto CTEP phase I trials has improved over time by virtue of, for example, more stringent enrollment criteria and the initiation of dedicated renal dysfunction trials (excluded from our analysis), other factors may explain this trend. It is important to note that the C-G formula uses weight as a covariate input to estimate CrCl. Our demographic data confirm that weight and BSA have also increased over time (Appendix Tables A4 and A6). The average patient enrolled onto CTEP trials is no longer 70 kg and 1.73 m², but 78.2 kg and 1.91 m². Assuming identical true kidney function, the average patient today would have their C-G kidney function falsely overestimated because of the average higher weight this patient would have, which is imputed into the C-G formula. This means that dosing calculations or patient eligibility assessments based on estimated CrCl as established in the past will not result in the same outcome today. Patients are, on average, heavier, have a higher estimated CrCl, will receive a higher dose, and will more likely meet minimum CrCl eligibility targets. Interestingly, the American Society of Clinical Oncology practice guidelines for obese patients suggests dosing carboplatin based on GFR because “carboplatin clearance is dictated by renal filtration, and GFR correlates with BSA.”²⁵ Our data suggest that in some patients extra weight (which covaries with BSA) results in a biased estimate of CrCl and GFR. On reviewing CrCl as estimated by Jelliffe over time, the trend of improving renal function, although still statistically significant, is indeed smaller in magnitude compared with the analysis based on C-G (Appendix Table A8), which is in line with the Jelliffe formulas not using an anthropomorphic size covariate, resulting in a BSA-normalized estimate of CrCl. Any residual changes in renal function over time may be a result of changes in patient selection and more stringent renal function eligibility criteria, which in some of the earlier CTEP-sponsored studies allowed an S_{Cr} of ≤ 2 mg/dL or $\leq 1.5 \times$ the institutional upper limit of normal. Analysis of the relationship between toxicity and CrCl calculated according to Jelliffe still yielded statistical significance (Appendix Table A10, online only), suggesting that the effect of BSA, which varies with time, did not represent a large bias.

The current data do not address the question of which formula to use to assess a patient's renal function, although the qualitative aspects of the renal function data are similar for all four formulas. The various

formulas have been compared with gold standard assays, such as iodine-125-iodothalamate, iothexol, technetium-99m-diethylene-triamine-pentaacetate, or chromium-51-edathamil,²⁶ and in general, the Jelliffe formula has a negative bias.^{27,28} Although MDRD is often reported to be slightly less biased in predicting measured GFR than C-G, differences are often small, and no estimation formula is perfect for each individual, especially when applied to oncology patients with extremes of age, weight, renal function, and comorbidities.^{29,30} In some situations, the formula is standardized. For example, the Gynecologic Oncology Group (now part of NRG Oncology) consistently used the Jelliffe formula and switched to the C-G formula when creatinine assays were recalibrated to an isotope dilution mass spectrometry-traceable reference, whereas other cooperative groups, such as CALGB (now Alliance for Clinical Trials in Oncology), consistently use C-G. The use of the MDRD formulas has not gained wide acceptance in oncologic practice, even though some have advocated its general application.³¹

Phase I studies of antineoplastics are performed in patients with advanced cancer and are designed to characterize the adverse event profile and to determine a recommended dose for phase II studies. Our data document that many patients with refractory malignancies have mildly compromised renal function as defined by the FDA. However, it seems that this condition does not have a major impact on setting the MTD. We argue for adopting the FDA categorization of patients in future oncology renal organ dysfunction trials and eliminating the mild renal dysfunction group, unless renal clearance is a major contributor to total clearance of the drug or pharmacologically active metabolite or is a determinant of the MTD.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

AUTHOR CONTRIBUTIONS

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Effect of Renal Dysfunction on Toxicity in Three Decades of Cancer Therapy Evaluation Program–Sponsored Single-Agent Phase I Studies

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Appendix

Table A1. Antineoplastic Agents Studied in CTEP-Sponsored Phase I Trials From 1979 to 2010

Agent	NSC No.
¹³¹ I-radiolabeled MoAb CC-49	620537
Benzaldehyde dimethane sulfonate (BEN, DMS612)	281612
Ispinesib (SB-715992)	727990
¹³¹ I-chimeric mouse/human B72.3 (human γ 4) monoclonal antibody	324338
17-(Allylamino)-17-demethoxygeldanamycin, tanespimycin	330507
177-Lutetium-labeled CC49	620537
17-Dimethylaminoethylamino-17-demethoxy-geldanamycin, alvespimycin hydrochloride	707545
1-Methyl-D-tryptophan	721782
2',3'-Dideoxyadenosine	98700
2-Chlorodeoxyadenosine, cladribine	105014
2-F-ara-AMP, fludarabine-5'-monophosphate, fludarabine	312887
2'-F-ara-deoxyuridine	678515
2-Methoxy estradiol	659853
2-Nitroimidazole	684681
4-(All- <i>trans</i> -retino-yl)aminophenol, fenretinimide	374551
4'-Deoxydoxorubicin, esorubicin	267469
4-Ipomeanol	349438
6-Hydroxymethylacylfulvene	683863
6-Thioguanine	752
7-Hydroxystaurosporine (UCN-01)	638850
90-Yttrium-labeled CC49	NF
9-Aminocamptothecin	603071
9-Aminocamptothecin colloidal dispersion formulation	603071
Acivicin (AT-125)	163501
Acodazole	305884
AD5CMV-P53, advexin	683550
All- <i>trans</i> -retinoic acid	122758
ALVAC-CEA (VCP248)	659643
ALVAC-CEA/B7.1 vaccine	674306
ALV-IL12	689514
Alvocodib, flavopiridol	649890
Amino flavone prodrug	710464
Aminothiadiazole	4728
Amonafide, nafidimide	308847
Anti-B4 blocked ricin	639185
Anti-epidermal growth factor receptor antibody RG83852	633416
Batracylin	320846
Benzoylphenylurea	639829
Beta interferon	605606
Bizelesin	615291
BMS-275291, rebimastat	713763
Bortezomib	681239
Bromodeoxyuridine	38297
Bryostatin-1	339555
Caracemide	253272
Carboplatin	241240
Carboxy-amino-imidazole	609974
CDDO (triterpenoid)	NF

(continued on following page)

Renal Function in Phase I Patients

Table A1. Antineoplastic Agents Studied in CTEP-Sponsored Phase I Trials From 1979 to 2010 (continued)

Agent	NSC No.
Chimeric monoclonal anti-GD2 antibody 14.18	623408
Chloroquinoxaline sulfonamide	339004
Cilengitide	707544
Cisplatin	119875
COL3	683551
Cyclopentenyl cytosine	375575
Decitabine, 5-aza-2 deoxycytidine	127716
Deoxyspergualin	356894
Depsipeptide	630176
Diaziquone	182986
Didemnin-B	325319
Dihydrofenperone	343513
Docetaxel	628503
Dolastatin-10	376128
Doxorubicin	123127
Endostatin	704805
Entinostat, HDAC inhibitor SNDX-275	706995
Erb-38 immunotoxin	683039
Farnesyltransferase inhibitor BMS-214662	710086
Farnesyltransferase inhibitor, zarcesta	702818
Fazarabine	281272
Flavone acetic acid	347512
Fostriecin	339638
Gallium nitrate	15200
Gamma interferon	600662
GI-6207 Tarmogen	NF
GM-CSF	613795
Halichondrin B analog	707389
Hexamethylene biscacetamide	95580
Hexamethylmelamine	13875
Homoharringtonine, omacetaxine mepesuccinate	141633
HuM291 (humanized anti-CD3 monoclonal antibody)	711007
Humanized 1D10 MoAb	704867
Hydroxyurea	32065
ICI D1694	639186
Imatinib	716051
Indimitecan (LMP776)	725776
Indotecan (LMP400)	743400
Interleukin-12 DNA	709933
Interleukin-1	621381
Interleukin-2	NF
Interleukin-3	641115
Interleukin-4	618085
Interleukin-6	643497
Interleukin-12	672423
¹³¹ I-labeled COL-1	NF
Ipilimumab (MDX-010/MDX-TRAN)	732442/72081
Iproplatin	256927
Irinotecan	616348
Ixabepilone, BMS-247550	710428
KNI-272	651714
KRN5500	650426
L-Buthionine sulfoximine	326231
Liposomal doxorubicin	620212
LMB-2 immunotoxin, anti-tac (FV)-PE-38	676422
LMB-7 immunotoxin, LMB-7, B3 (FV)-PE-38	658931
LMB-9 immunotoxin	691236
Macrophage colony-stimulating factor (M-CSF)	625377

(continued on following page)

Table A1. Antineoplastic Agents Studied in CTEP-Sponsored Phase I Trials From 1979 to 2010 (continued)

Agent	NSC No.
MAGE-1 vaccinia vaccine	658894
MART-1	672643
MEDI-522 (monoclonal antibody anti-alpha V beta 3 integrin)	719850
Menogaril	269148
Mitoxantrone	301739
MoAb anti-B4/blocked ricin immunoconjugate	NF
MoAb anti-CD3	NF
MoAb HEFI-1 (anti-cd30)	603573
MoAb xomazyme-65	NF
Monoclonal antibody HCC49DCH2	696081
Motexafin gadolinium	695238
Mouse monoclonal anti-T suppressor cell (anti-leu 2a) antibody	NF
Murine anti-GD3 monoclonal antibody, MG-22	NF
Murine MoAb T101	NF
Murine monoclonal antibody D6.12	641116
Murine monoclonal antibody HD37 deglycosylated ricin A chain conjugate	639181
Murine monoclonal anti-GD2 antibody 14G2a	624345
Mutant p53 peptides	NF
Mutant ras peptides	NF
<i>n</i> -Methylformamide	3051
ONYX-015 (dl1520, CI-1042, E1B 55 kDa-gene-deleted, replicative adenovirus)	NF
Orantinib (SU6668)	702827
Oxaliplatin	266046
Paclitaxel	673089
Papillomavirus 16 E6 peptide	673924
Papillomavirus 16 E7 peptide	673925
Pazopanib	737754
PCNU	95466
Penclomedine	338720
Pentosan	626201
Perifosine	639966
Perillyl alcohol	641066
Phenylbutyrate	657802
Pibenzimol	322921
Poly-ICLC	301463
Prioxantrone, oxantrazole	349174
Pyrazine diazohydroxide	361456
Pyrazoloacridine	366140
Quinocarmycin analogue	607097
R(+)-XK469	698215
R24 monoclonal antibody	608918
Ras peptide gly to asp	667938
Ras peptide gly to cys	667937
Ras peptide gly to val	665824
Rebeccamycin analogue	655649
Recombinant fowlpox-PSA/Tricom	717171
Recombinant NYCBOH vaccinia virus with carcinoembryonic antigen gene (rV-CEA)	649024
Recombinant vaccinia expresses DF3/MUC1	694449
Recombinant vaccinia/CEA-CV-1	678893
Reolysin	729968
RF-B7.1 vaccine	679008
RO4929097	749225
RV-B7.1 vaccine	699018
Sarcosinamide nitrosourea	364432
SJG136	694501
Spiromustine	172112
Sulfamic acid	329680
Suramin	34936
Temozolomide	362856
Temsirolimus	683864

(continued on following page)

Renal Function in Phase I Patients

Table A1. Antineoplastic Agents Studied in CTEP-Sponsored Phase I Trials From 1979 to 2010 (continued)

Agent	NSC No.
Terephthalamidine	57155
Tetraplatin, ormaplatin	363812
Tiazofurin (TCAR)	286193
TNP-470	642492
Topotecan	609699
Triapine (3AP)	663249
Tributylin	661583
Triciribine phosphate	280594
Trimethylcolchicinic acid	36354
Trimetrexate	352122
Tumor necrosis factor	635257
Veliparib (ABT-888)	737664
Vorinostat (SAHA)	701852

Abbreviations: CTEP, Cancer Therapy Evaluation Program; GM-CSF, granulocyte-macrophage colony-stimulating factor; HDAC, histone deacetylase; ¹³¹I, iodine-131; NF, not found; MoAb, monoclonal antibody; NSC, National Service Number.

Table A2. Age (years) As a Function of Time

Study Year	No. of Patients	Age (years)				
		Mean	Median	Standard Deviation	Minimum	Maximum
1979-1984	698	54.2	56	12.2	20	85
1985-1989	1,809	54.7	57	12.7	18	83
1990-1994	2,724	56.6	58	12.5	18	90
1995-1999	2,156	55.5	56	12.7	20	88
2000-2004	1,738	57.4	58	12.9	18	96
2005-2010	1,111	57.4	59	12.7	19	85
All	10,236	56.1	57	12.7	18	96

Table A3. Sex As a Function of Time

Study Year	No. of Patients	Sex (% male)
1979-1984	698	55.2
1985-1989	1,809	61.1
1990-1994	2,724	61.2
1995-1999	2,156	57.5
2000-2004	1,738	57.8
2005-2010	1,111	54.1
All	10,236	58.7

Table A4. Weight As a Function of Time

Study Year	No. of Patients	Weight (kg)				
		Mean	Median	Standard Deviation	Minimum	Maximum
1979-1984	698	68.5	67.0	16.8	29.3	167
1985-1989	1,809	71.9	70.4	17.1	25.3	184
1990-1994	2,724	75.2	74.3	17.2	33.9	188
1995-1999	2,156	78.0	76.8	19.7	31.1	233
2000-2004	1,738	78.3	76.9	18.6	35.7	179
2005-2010	1,111	78.2	75.5	19.8	36.9	182
All	10,236	75.6	74.0	18.5	25.3	233

Table A5. Height As a Function of Time

Study Year	No. of Patients	Height (cm)				
		Mean	Median	Standard Deviation	Minimum	Maximum
1979-1984	659	169.3	170.0	10.5	115.0	198.0
1985-1989	1,780	170.1	170.0	10.0	117.0	200.0
1990-1994	2,669	170.7	170.2	10.0	108.1	196.7
1995-1999	2,099	170.3	170.2	10.8	100.5	198.1
2000-2004	1,719	169.8	170.2	10.5	106.7	203.0
2005-2010	1,109	169.5	169.4	9.7	144.0	201.0
All	10,035	170.1	170.1	10.3	100.5	203.0

Table A6. Calculated BSA As a Function of Time

Study Year	No. of Patients	BSA (m ²)				
		Mean	Median	Standard Deviation	Minimum	Maximum
1979-1984	659	1.78	1.77	0.25	1.10	2.93
1985-1989	1,780	1.83	1.82	0.24	1.08	2.87
1990-1994	2,669	1.88	1.88	0.24	1.17	2.96
1995-1999	2,099	1.91	1.90	0.26	1.17	3.41
2000-2004	1,719	1.91	1.91	0.26	1.22	2.94
2005-2010	1,109	1.91	1.89	0.27	1.22	3.00
All	10,035	1.88	1.87	0.25	1.08	3.41

Abbreviation: BSA, body-surface area.

Table A7. Race As a Function of Time

Study Year	No. of Patients	Race (% of patients)				
		White	Black/AA	NH/OPI	Asian	AI/AN
1995-1999	1,630	88.9	8.8	0.2	2.0	0.1
2000-2004	1,437	89.5	7.7	0.4	2.2	0.2
2005-2010	1,017	86.2	9.4	0.2	4.0	0.1
All	4,084	88.4	8.6	0.3	2.5	0.1

Abbreviations: AA, African American; AI/AN, American Indian or Alaskan native; NH/OPI, native Hawaiian or other Pacific Islander.

Renal Function in Phase I Patients

Table A8. Jelliffe-Calculated CrCl As a Function of Time

Year	NCI/CALGB Criteria					FDA Criteria				
	No. of Patients	% of Patients				No. of Patients	% of Patients			
		Severe: CrCl < 20 mL/min/1.73 m ²	Moderate: CrCl 20-39 mL/min/1.73 m ²	Mild: CrCl 40-59 mL/min/1.73 m ²	Normal: CrCl ≥ 60 mL/min/1.73 m ²		Severe: CrCl < 30 mL/min/1.73 m ²	Moderate: CrCl 30-49 mL/min/1.73 m ²	Mild: CrCl 50-79 mL/min/1.73 m ²	Normal: CrCl ≥ 80 mL/min/1.73 m ²
1979-1984	698	0.14	3.58	26.1	70.2	698	1.00	12.3	51.0	35.7
1985-1989	1,809	0.61	4.81	27.9	66.7	1,809	1.22	15.37	54.1	29.4
1990-1994	2,724	0.11	4.19	34.8	60.9	2,724	0.59	17.33	58.0	24.1
1995-1999	2,156	0.14	2.83	23.6	73.4	2,156	0.28	10.76	50.8	38.1
2000-2004	1,738	0.35	3.34	26.6	69.7	1,738	0.75	12.95	50.4	35.9
2005-2010	1,111	0.09	3.69	21.2	75.0	1,111	0.54	11.4	46.4	41.6
Trend over time, <i>P</i> *	< .001					< .001				

Abbreviations: CALGB, Cancer and Leukemia Group B; CrCl, creatinine clearance; FDA, US Food and Drug Administration; NCI, National Cancer Institute.

*Trend over time by Jonckheere-Terpstra test.

Table A9. Toxicity As a Function of Cockcroft-Gault CrCl

Toxicity	NCI/CALGB Criteria					FDA Criteria				
	% of Patients Experiencing Toxicities				<i>P</i> *	% of Patients Experiencing Toxicities				<i>P</i> *
	Severe: CrCl < 20 mL/min (n = 14)	Moderate: CrCl 20-39 mL/min (n = 201)	Mild: CrCl 40-59 mL/min (n = 1,285)	Normal: CrCl ≥ 60 mL/min (n = 7,265)		Severe: CrCl < 30 mL/min (n = 41)	Moderate: CrCl 30-49 mL/min (n = 645)	Mild: CrCl 50-79 mL/min (n = 3,131)	Normal: CrCl ≥ 80 mL/min (n = 4,948)	
Grade 3 nonhematologic	14.3	15.4	14.7	14.2		22.0	14.9	13.7	14.5	
Grade 4 nonhematologic	0.0	2.0	4.4	3.4		2.4	4.0	3.7	3.3	
Grade 3 or 4 nonhematologic	14.3	17.4	19.1	17.6	.198	24.4	18.9	17.4	17.8	.631
Grade 4 hematologic	7.1	12.4	10.6	8.7	.026	14.6	12.7	9.3	8.3	.155
Grade 5	0.0	0.5	0.8	0.3		0.0	1.1	0.4	0.3	
Any	21.4	26.9	26.4	23.8	.045	39.0	27.3	24.1	23.8	.778

NOTE. Denominator is number of patients enrolled onto trials where any grade 4 hematologic, grade 3 or 4 nonhematologic, or grade 5 toxicities occurred. For nonhematologic toxicity, only the highest grade toxicity was counted for each patient. Every patient was counted once in each of the following three categories when listed separately: grade 3 or 4 nonhematologic, grade 4 hematologic, and grade 5 toxicity. For any toxicity, each patient was only counted once.

Abbreviations: CALGB, Cancer and Leukemia Group B; CrCl, creatinine clearance; FDA, US Food and Drug Administration; NCI, National Cancer Institute.

*Mild v normal.

Table A10. Toxicity As a Function of Jelliffe CrCl

Toxicity	NCI/CALGB Criteria					FDA Criteria				
	% of Patients Experiencing Toxicities				<i>P</i> *	% of Patients Experiencing Toxicities				<i>P</i> *
	Severe: CrCl < 20 mL/min/1.73 m ² (n = 4)	Moderate: CrCl 20-39 mL/min/1.73 m ² (n = 134)	Mild: CrCl 40-59 mL/min/1.73 m ² (n = 935)	Normal: CrCl ≥ 60 mL/min/1.73 m ² (n = 2,325)		Severe: CrCl < 30 mL/min/1.73 m ² (n = 23)	Moderate: CrCl 30-49 mL/min/1.73 m ² (n = 454)	Mild: CrCl 50-79 mL/min/1.73 m ² (n = 1,782)	Normal: CrCl ≥ 80 mL/min/1.73 m ² (n = 1,139)	
Grade 3 nonhematologic	25.0	24.6	22.5	20.5		13.0	23.8	21.1	20.5	
Grade 4 nonhematologic	0.0	9.0	7.6	5.2		8.7	9.7	5.8	4.7	
Grade 3 or 4 nonhematologic	25.0	33.6	30.1	25.6	.010	21.7	33.5	26.9	25.2	.312
Grade 4 hematologic	25.0	10.4	14.2	12.8	.268	21.7	12.1	13.1	13.3	.922
Grade 5	0.0	0.7	1.3	0.4		4.3	1.5	0.6	0.3	
Any	50.0	40.3	38.8	34.0	.009	39.1	41.9	35.1	33.8	.48

NOTE. Denominator is number of patients enrolled onto top two dose levels of trials where any grade 4 hematologic, grade 3 or 4 nonhematologic, or grade 5 toxicities occurred. For nonhematologic toxicity, only the highest grade toxicity was counted for each patient. Every patient was counted once in each of the following three categories when listed separately: grade 3 or 4 nonhematologic, grade 4 hematologic, and grade 5 toxicity. For any toxicity, each patient was only counted once.

Abbreviations: CALGB, Cancer and Leukemia Group B; CrCl, creatinine clearance; FDA, US Food and Drug Administration; NCI, National Cancer Institute.

*Mild v normal.

Fig A1. Distribution of the creatinine clearance calculated by all four methods: (A) Cockcroft-Gault, (B) Jelliffe, (C) six-variable Modification of Diet in Renal Disease (MDRD6), and (D) four-variable modification (MDRD4). BSA, body-surface area; FDA, US Food and Drug Administration; NCI, National Cancer Institute.