GFR Measurement and Chemotherapy Dosing in Patients with Kidney Disease and Cancer

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Abstract
Chemotherapeutic agents require precise dosing to ensure optimal efficacy and minimize complications. For those agents that are removed from the body by the kidney, accurate knowledge of GFR is critical. In addition, GFR needs to be determined rapidly, easily, and, if possible, with little additional cost. The ability to easily measure GFR also allows for rapid detection of nephrotoxicity. Current methodologies include direct clearance measurement of an indicator substance or estimation of creatinine clearance or GFR through regression equations that use a serum marker, such as creatinine or cystatin C. These methodologies all have shortcomings and limitations, some of which are specific to the patient with cancer. Newer methodologies that directly measure GFR are in clinical trials and offer the ability to rapidly and noninvasively provide accurate estimates of drug clearance as well as detection of nephrotoxicity. These methods offer the opportunity to refine drug dosing and improve outcomes.

Introduction
Chemotherapeutic agents used to treat cancer generally have narrow therapeutic indices along with potentially serious adverse toxicities. Accurate dosing is required to ensure optimal outcomes and to avoid toxicity. For those drugs excreted through the kidney, a precise understanding of kidney function is needed to ensure achievement of therapeutic levels and avoidance of these toxicities. In general, two pathways are involved in the excretion of drugs and their metabolites by the kidney: glomerular filtration and tubular secretion. Glomerular filtration is relevant for smaller, non-protein-bound substances. Tubular secretion is a more common pathway for protein-bound compounds. In addition, tubular reabsorption of a drug can also occur, which can raise the concentration of the drug. In most cases, the best measure of kidney function is the GFR, which has generally been accepted as a measure of functioning kidney mass (1). In addition, measures to directly and indirectly measure GFR have been well validated, and there is extensive experience with their operational characteristics (1). Although measurement of tubular secretion can be performed, it is more laborious and of unclear clinical significance (1).

Some of the chemotherapeutic agents that are, at least partially, excreted through the kidney include capecitabine, etoposide, carboplatin, cisplatin, mitomycin, methotrexate, pemetrexed, pentostatin, topotecan, bleomycin, and others (2). In fact, carboplatin is unique among chemotherapeutic agents in that its dosing is largely on the basis of determination of eGFR (3). For many other drugs, dosing guidelines in the setting of impaired kidney function are either nonexistent or only loosely evidence based (4–6). Although in some cases, drug levels can be measured and dosing can be adjusted to reach therapeutic levels (such as with methotrexate and cyclophosphamide), in other cases this is more difficult or is not feasible (7). An example of the benefit of more personalized dosing strategies on the basis of the measurement of drug levels was a study by McCune et al. (8) where personalized therapeutic drug monitoring of cyclophosphamide dosing parameters was used in patients undergoing hematopoietic stem cell transplantation. In those patients with personalized cyclophosphamide dosing, there was improved liver function, lower incidence of AKI (by 38%), and similar rates of nonrelapse and overall survival (8).

This article focuses on the various methodologies that are available to assess kidney function in patients with cancer, with the aim of leading to more accurate chemotherapeutic drug dosing as well as rapid detection of nephrotoxicity. Each methodology has limitations in the patient with cancer. For instance, the use of serum creatinine as a measure of GFR in patients with cancer may be influenced by poor dietary intake of protein, muscle wasting, malnutrition, changes in hydration, and liver disease that are prevalent in these patients (1). As an example of this, Launay-Vacher and colleagues (9,10) found that an abnormal serum creatinine was seen in <10% of patients with cancer, whereas an abnormal GFR was seen in a much higher percentage (approximately 50%). In fact, it may be the case that patients with cancer more often present with abnormal GFRs than normal levels of kidney function. For instance, only 38.6% of patients with breast cancer, 38.9% of patients with lung cancer, 38.3% of patients with prostate cancer, 27.5% of patients with gynecologic cancer, and 27.2% of patients with colorectal cancer...
cancer had a GFR≥90 ml/min per 1.73 m² at the time of therapy initiation (9,11–13).

The Effect of Impaired GFR on Chemotherapeutic Pharmacokinetics and Drug Toxicity

The effects of kidney disease may affect aspects of pharmacokinetics of cancer drugs that are unexpected and beyond simple urinary excretion. Recently, the Food and Drug Administration (FDA) published a guidance document for industry regarding the new requirements for pharmacokinetic studies in patients with impaired GFR. The FDA recommends that pharmacokinetic studies in kidney impairment models be conducted for medications that are not renally eliminated, recognizing the fact that nonrenal clearance mechanisms can be altered in patients with impaired kidney function (14).

As an example of this, a lower absorption rate of sunitinib was observed in patients with reduced kidney function compared with patients with normal function (15). In addition, the volume of distribution of a drug is significantly affected by serum protein binding. In patients with hypoalbuminemia (from nephrotic syndrome or poor nutritional status), the free fraction of some drugs may be increased, leading to altered kinetics and actions. Development of toxicity has been observed in patients receiving cisplatin plus paclitaxel chemotherapy in those patients with lung cancer who have malnutrition and low albumin levels (16). In those patients with significantly impaired kidney function, uremic toxins can compete with drugs for plasma protein-binding sites, also leading to altered pharmacokinetics (17). However, despite these established alterations in the pharmacokinetics of a cancer drug in patients with impaired kidney function, the single most important factor to understand in patients with kidney disease is the effect of a diminished GFR on the elimination phase for a cancer drug. As an estimation of the magnitude of this issue, in the Insuffisance Rénale et Médicaments Anticancéreux (Renal Insufficiency and Anticancer Medications) studies, 79.9% of the patients received at least one drug that required dose modification for kidney function, and 80.1% of the patients received at least one anticancer drug with significant nephrotoxicity risk potential (18,19).

The effect of the failure to recognize impaired kidney function is critically important (20). In a study of patients with metastatic colon cancer receiving a combination of capecitabine and oxalaplatin, patients were dosed on the basis of their serum creatinine values that were in the “normal” range (20). Patients were then stratified on the basis of creatinine clearance as determined by the Cockcroft and Gault formula. In doing so, they identified 35% of patients with a creatinine clearance <60 ml/min (despite “normal” serum creatinine values). Drug toxicity, including cytopenias; stomatitis; diarrhea; and hand-foot syndrome were much more common in the group with unidentified kidney disease. Alternatively, in a recent trial of cyclophosphamide and doxorubicin or cyclophosphamide, methotrexate and fluorouracil over capecitabine in women with early stage breast cancer, the measurement of kidney function with the Cockcroft and Gault formula and subsequent dosing alterations led to equivalent outcomes and similar rates of complications in the groups with kidney disease and those without (21). This highlights that the use of kidney function measurements and appropriate dose modifications can improve outcomes.

Methodologies Using Exogenous Markers to Measure GFR

Measurement of GFR can be cumbersome and time consuming. Thus, in general, serum markers (such as creatinine and cystatin C) have been developed to be used in GFR estimating equations (see below). In some circumstances, more precise determination of GFR is needed, and then, urinary clearance of an ideal filtration marker can be measured. Clearance is the rate at which an indicator substance is removed from the plasma and specifies a volume from which all of a substance is removed per unit time: for a substance X, clearance = urinary concentration of x (Ux) multiplied by the urine flow rate (V)/plasma concentration of X (Fp). For an ideal substance that is freely filtered by the glomerulus undergoing no tubular reabsorption, excretion, or metabolism and thus, only excreted by GFR, GFR = (Ux) × (V/Fp). Thus, for indicator x, its plasma concentration is inversely related to GFR.

Typically, methodologies for the use of exogenous markers for the measurement of GFR rely on urine collections with time-averaged plasma concentrations of the exogenous marker. GFR can be determined by either a bolus or continuous infusion of the marker. There are several exogenous markers that can be used for determination of GFR. Inulin, with a molecular mass of 5000 D, is a freely filtered fructose polymer that is physiologically inert and meets many criteria for being an ideal marker for GFR measurement (1). However, timed collections are laborious, the compound is poorly soluble and is not readily available, and assays for its measurement are not widely accessible (22). Other markers include radionuclides and radiocontrast agents where clearance can be determined as the amount of indicator injected divided by the integrated area of plasma concentration curve over time (1). The most commonly used radionuclide agents include 125I-iothalamate and 51Cr-EDTA (detected by plasma levels) or 99mTcm-captatoetiltilglycine and 99mTc-diethyliodamine penta-acetic acid (detected by γ-counter) (23). Radiocontrast markers include iohekol and diatrizoate meglumine, which are often determined by high-performance liquid chromatography (24). Radionuclide and radiocontrast methodologies, although accurate, are also not widely available, are time and labor intensive, and can be associated with adverse events, such as radiation exposure and risk for anaphylaxis. Thus, these methodologies are typically not used in daily patient-specific clinical decision making. Their role in oncology may be to provide confirmation of GFR values obtained through other techniques, to determine GFR in situations where there is clinical uncertainty (such as nonsteady-state conditions or at extremes of body mass), or in more formal research settings.

Methodologies Using Endogenous Markers to Measure GFR

Creatinine

Serum creatinine has been used to estimate the GFR on the basis of several assumptions: (1) creatinine is freely
filtered at the glomerulus and thus, excreted by glomerular filtration, and (2) creatinine production and excretion are constant in the steady state. Although it is generally true that a rise in serum in creatinine generally reflects a fall in GFR, due to a myriad of factors, serum creatinine levels only roughly track with GFR due to factors, such as age, muscle mass, meat intake, and race. Thus, either GFR estimation equations (which adjust for some of these confounding factors) or creatinine clearance must be used to best assess GFR. As described above, creatinine clearance can be calculated with a plasma measurement and timed urine collection (such as for 24 hours). When comparing a patient’s creatinine clearance with normal values to assess for the presence of kidney disease, the value should be adjusted to body surface area (BSA). However, for the purpose of drug dosing, the unadjusted creatinine clearance is typically used. The lack of standardization around the utilization of clearance indexed to BSA or not is critically important, and clinicians and researchers need to pay special attention to the reporting of clearance values to ensure that they are comparing similar estimates of kidney function. However, creatinine clearance is not routinely used in clinical practice or clinical trials (due to difficulty in obtaining a 24-hour urine collection and lack of real-time results). Furthermore, creatinine clearance does not improve estimates of GFR over those provided by estimation equations using serum creatinine (see below). In addition to collection errors with capturing the timed urine collection, diurnal variation in GFR and day-to-day variation in creatinine excretion may also contribute to the errors in GFR estimation with timed urine collection (25,26).

Further compounding the accuracy of using creatinine for GFR measurements is that creatinine production is influenced by variables, such as age, sex, nutritional status, muscle mass, and intake of creatine supplements. In addition, a significant proportion (10%–40%) of creatinine excretion in the urine is due to proximal tubular secretion, which can lead to erroneous overestimation of GFR if only the serum creatinine is used (27). This is critically important early in the course of kidney disease, where the early fall in GFR and the rise in serum creatinine may be mitigated by rises in proximal tubular secretion of creatinine. Thus, clinically significant falls in GFR that may affect drug clearance may not be detectable by rises in serum creatinine. In fact, one study showed that, among patients with cancer and normal serum creatinine measurements, one of five patients had asymptomatic kidney insufficiency as assessed by a standard creatinine clearance method (28). This secretory pathway can also be inhibited by drugs, such as cimitidine, trimethoprim, duloxetine, and others, which leads to false elevations in serum creatinine that do not reflect true falls in GFR. Importantly, many oncology patients may also not be in the steady state (where creatinine production and excretion are equalized) due to acute illness with fluctuations in their daily nutritional intake, changes in muscle mass due to cachexia, and alterations in body hydration.

Another confounding issue with the use of serum creatinine–based GFR measurements relates to variability in laboratory creatinine measurement (29). Currently, laboratories trace creatinine reference levels to isotope dilution mass spectrometry–assigned values to reduce interlaboratory variability and improve assay accuracy (30). Despite this, a recent study showed that the mean±SD of creatinine measurements was 0.20±0.09 mg/dl with the Jaffe assay, yielding higher creatinine values than enzymatic assays (30). These variations should be considered in the assessment of GFR, and repeat measurements of creatinine should be obtained in unclear situations.

Finally, serum creatinine is an insensitive indicator of kidney function in that patients can lose significant amounts of GFR without changes in creatinine values and that the changes in serum creatinine can lag 24–72 hours after a kidney insult (28–30). Similarly, some patients with cancer and recovered AKI can have a “normal” serum creatinine after their AKI but now have diminished renal reserve. Renal functional reserve describes the capacity of the intact nephron mass to increase GFR from baseline in response to physiologic and noxious stimuli, and it can be calculated by using endogenous creatinine clearance corrected for BSA with the use of the Dubois method. Basal renal functional reserve can predict future risk of AKI in patients with stomach cancer (31), and it may provide an opportunity to risk stratify high-risk patients with AKI prior to future cancer treatments and to increase the frequency of laboratory monitoring of renal function during cancer treatment.

Important exceptions when timed 24-hour collections are useful may be the estimation of GFR in individuals with variations in dietary intake (vegetarian diet or creatine supplements) or muscle mass (amputation, malnutrition, or muscle wasting) because these factors are not specifically taken into account in prediction equations (see below). In these situations, collection of a 24-hour urine sample for measurement of creatinine clearance or measurement of clearance of an exogenous filtration marker may provide better estimates of GFR than prediction equations.

Cystatin C

Cystatin C is 13,000-D cysteine proteinase inhibitor produced by all nucleated cells at a constant rate. It is freely filtered at the glomerulus, and then, it undergoes catabolism within the kidney tubules, resulting in no urinary excretion. Thus, the serum level of cystatin C depends on GFR, and it can be used as a measure of kidney function (32,33). Measurement of cystatin C is by particle-enhanced nephelometric immunoassay. It has been reported that cystatin C levels are not affected by sex, age, race, protein intake, or muscle mass, and thus, it may have enhanced accuracy over serum creatinine in determination of GFR (34–37). However, this is widely debated, and data from several studies have documented variations in cystatin C levels associated with sex, lean body mass, height, weight, thyroid disease, and other conditions (37–40). In addition, there are variations in the laboratory measurement and reporting of cystatin C levels that further confound its use (41). Within oncology, the use of isolated cystatin C measurements for the determination of GFR and detection of nephrotoxicity has been questioned because there seem to be independent effects of both the malignancy and chemotherapy on cystatin C levels, which confound its utility (42–44). Thus, cystatin C measurements alone are not appropriate for measurement of kidney function or for detection of nephrotoxicity.

Estimation of GFR through Regression Equations

Estimation of GFR is typically through various regression equations that may include creatinine clearance estimation,
Creatinine Clearance Estimation

The estimation of creatinine clearance regression methodologies was first described in the 1950s. Estimated creatinine clearance is typically reported in milliliters per minute and is not equal to GFR (reported in millimeters per minute per 1.73 m²), although it is often used as a surrogate for GFR (46).

Creatinine clearance estimates have evolved to include the Cockcroft and Gault (47), Jelliffe (48), and Wright et al. (49) formulas. These formulas use patient characteristics, such as weight, age, sex, and serum creatinine (Table 1), but fail to incorporate several other non-GFR determinants of serum creatinine, including diet, race, tubular secretion, and extrarenal elimination of creatinine, and they may no longer provide accurate estimates (50). In addition, these equations were developed before standardization of creatinine assays, overestimating GFR up to 10%–20% and therefore, predisposing many patients with cancer to unnecessary toxicities. Therefore, these estimates run the risk of misassigning a patient to an incorrect category of GFR, resulting in potential therapeutic management errors. Of note, some chemotherapeutic drugs are dosed not by dose modification for changes in kidney function but instead, on the basis of threshold kidney function values below which the drug should not be dosed. For example, recommendations for pemetrexed preclude administration if the kidney function is <45 ml/min. Thus, misassigning a GFR value to a patient may result in that patient either not being given an effective chemotherapy or being given an effective chemotherapy inappropriately (51). Despite this fact, almost half of all active clinical trials involving chemotherapeutic drugs use kidney function thresholds defined by serum creatinine alone or a composite of serum creatinine or creatinine clearance. In one comprehensive study of all active phases 1–3 cisplatin trials obtained from the www.clinicaltrials.gov website, 212 of 465 studies (46%) used serum creatinine alone or a composite of serum creatinine or creatinine clearance, and many trials had inadequate information on kidney function thresholds (52).

eGFR Measurements

In an effort to improve kidney function measurement and address some of the shortfalls in creatinine clearance estimation, the Modification of Diet in Renal Disease (MDRD)
similar levels of concordance in dosage of carboplatin when 
apy dose was determined. All bedside formulas result in 
formulas (56). Assessment of concordance with chemother-
EPI, the Cockcroft and Gault, the Wright, and the Martin 
function estimates using the four-variable MDRD, the CKD-
was measured using 99mTc-DPTA and compared with renal 
ction has been shown to be superior to the performance of the 
other methodologies (51,55). In addition, the MDRD equa-
EPI equation in the population of patients with cancer over 
should be exercised. However, over the past 3 years, several 
extrapolation of these equations to this patient population 
eGFR equations were derived, and thus, some caution in 
ance in the patient cohorts from which these 
eGFR equations were derived, and thus, some caution in 
filtration marker 
generation 
Body mass 
Race/ethnicity 
Diet 
Nutritional status 
Catabolic states 
Ingestion of cooked meats 
Rhabdomyolysis 
Clearance by RRT 
Decreased by inhibition of gut creatininases by antibiotics 
Increased by insensible losses 
Assay interference 
Filtration marker generation 
Body mass 
Race/ethnicity 
Diet 
Nutritional status 
Catabolic states 
Ingestion of cooked meats 
Rhabdomyolysis 
Clearance by RRT 
Decreased by inhibition of gut creatininases by antibiotics 
Increased by insensible losses 

Table 2. Some factors that may influence serum creatinine and cystatin C measurements

<table>
<thead>
<tr>
<th>Factors</th>
<th>Serum Creatinine</th>
<th>Serum Cystatin C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Filtration marker generation</td>
<td>Body mass</td>
<td>Increased by corticosteroids</td>
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<tr>
<td></td>
<td>Race/ethnicity</td>
<td>Increased in hyperthyroidism</td>
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<td></td>
<td>Diet</td>
<td>Decreased in hypothyroidism</td>
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<tr>
<td>Nonrenal elimination</td>
<td>Clearance by RRT</td>
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<tr>
<td></td>
<td>Decreased by inhibition of gut creatininases by antibiotics</td>
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</tr>
<tr>
<td></td>
<td>Increased by insensible losses</td>
<td></td>
</tr>
<tr>
<td>Inhibition of tubular secretion</td>
<td>Cimetidine, ranitidine</td>
<td>None</td>
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<td></td>
<td>Fenofibrate</td>
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<tr>
<td></td>
<td>Trimeprprim</td>
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<td>Albumin</td>
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<td></td>
<td>Dolutegravir</td>
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<tr>
<td></td>
<td>Cisplatin</td>
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<tr>
<td></td>
<td>Flucytosine</td>
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<tr>
<td>Assay interference</td>
<td>Drugs (flucytosine, barbiturates, some cephalosporins, N-acetylcysteine, some</td>
<td>None</td>
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<tr>
<td></td>
<td>catecholamines [such as dopamine, dobutamine]</td>
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</tr>
<tr>
<td></td>
<td>Others (bilirubin, ketones, glucose)</td>
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(53) and more recently, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations (53) were developed. The CKD-EPI equation is currently recommended by the National Kidney Foundation–Kidney Disease Outcome Quality Initiative and the Kidney Disease Improving Global Outcomes (KDIGO) guideline groups (KDIGO guidelines CKD 2012). In comparison with estimates of creatinine clearance, such as the Cockroft and Gault equation, the MDRD and CKD-EPI equations estimate GFR and incorporate race (black versus other) and sex but not weight (Table 2). The CKD-EPI and MDRD study equations are designed for use with a standardized serum creatinine assay and have been validated in cohort studies of patients with cancer (54).

The CKD-EPI equation is more accurate than the MDRD study equation, especially at higher GFRs (>60 ml/min per 1.73 m²), and this accounts for the preference in its use over the MDRD equation (55). Various CKD-EPI equations can be used with serum creatinine, serum cystatin C, or combination of both values. Of note, patients with cancer were not well represented in the patient cohorts from which these eGFR equations were derived, and thus, some caution in extrapolation of these equations to this patient population should be exercised. However, over the past 3 years, several publications have shown superior performance of the CKD-EPI equation in the population of patients with cancer over other methodologies (51,55). In addition, the MDRD equation has been shown to be superior to the performance of the Cockroft and Gault equation when applied to patients receiving chemotherapy (56,57). This was nicely demonstrated in one study of 455 adult oncology patients whose GFR was measured using 99mTc-DPTA and compared with renal function estimates using the four-variable MDRD, the CKD-EPI, the Cockroft and Gault, the Wright, and the Martin formulas (56). Assessment of concordance with chemotherapy dose was determined. All bedside formulas result in similar levels of concordance in dosage of carboplatin when compared with a direct measure of renal function. All formulas resulted in carboplatin dosing of more than ±20% of target dose in a fifth of all patients. However, the Cockroft and Gault equation (with ideal body weight) was the least concordant, and it was significantly discordant in obese patients (body mass index >30 kg/m²), resulting in underdosing of carboplatin (56). This explains the superiority of the MDRD and CKD-EPI equations over the Cockroft and Gault formula; it is significantly less accurate in patients with extremes of body mass, a situation that is not uncommon in many patients with cancer (10,50,54). Furthermore, many chemotherapeutic drugs are routinely dosed according to BSA, despite a growing body of evidence that there are significant limitations regarding BSA-based dosing of chemotherapeutic drugs. BSA dosing is associated with high pharmacokinetic variability, and it is a poor indicator of optimal drug exposure (58). The BSA indexing of estimated creatinine clearance (milliliters per minute per 1.73 m²) can alter dose classification of patients, and it can have implications for patient groups with BSAs that are significantly different from 1.73 m², ultimately resulting in inappropriate dose reductions or dose escalations (59,60).

More recent studies have compared the CKD-EPI equation with the MDRD and Cockroft and Gault equations and found that use of the CKD-EPI equation adjusted for surface body area was more accurate, demonstrated less bias (54), and may describe an eGFR that is more precise to true measured GFR compared with Cockroft and Gault equations. As with measured GFR, there are limitations to use of these equations to estimate GFR. There are various non-GFR parameters that affect filtration marker production, tubular reabsorption/secretion, nonrenal elimination, and assay interference that might contribute to a source of error in estimation of GFR in the general population. These issues are likely even more common in the patient with cancer (Table 2) (61) and include variable tubular creatinine secretion (59).
Furthermore, patients with cancer who are ill may be in a nonsteady-state condition where estimating equations are less likely to be accurate. These changes in GFR over time were demonstrated in a large retrospective evaluation of patients with solid tumors without CKD. Patients had an average decline in GFR of 7 ml/min per 1.73 m² after 2 years of diagnosis or a CKD stage decline from stage 2–3 or 4 (62). In another study, the risks of AKI were 17.5% and 27% in the first and fifth years of cancer diagnosis, respectively (63), demonstrating that GFR is changing in a substantial number of patients with cancer. Finally, estimating equations have been assessed in both adult and pediatric populations. In adults, all eGFR estimating equations gave reasonable estimates of GFR and can replace measured creatinine clearance with 24-hour urine collections (64). However, in a very limited number of pediatric studies with small study numbers, cystatin C-based equations outperformed creatinine-based equations in estimating GFR in children before hematopoietic stem cell transplant. However, all GFR estimating formulas have decreased sensitivity to detect impaired GFR and may suggest measurement of kidney function in children and young adults who need an accurate assessment of kidney function before HCT (65).

Cancer-Specific GFR Equations
Because of the potential errors in the estimation of eGFR in patients with cancer listed in Table 2, investigators have developed patients with cancer–specific eGFR formulas and drug-dosing equations from small cohorts of patients with cancer (2,49) (Table 1). One cancer-specific GFR equation is the Martin formula, which was assessed in 123 patients with mixed tumor types (66). This study used $^{51}$Cr-EDTA plasma clearance concentrations versus the time data of 80 patients. The formula was generated using a population pharmacokinetic approach using the nonlinear mixed effects model program (Table 1), and the formula was then validated in a separate group of 45 patients with cancer. Actual body weight was the most predictive factor, and it was more accurate that the Cockcroft and Gault equation (66). Similarly to the Martin formulas, the Wright formula was also developed via a population pharmacokinetic method of $^{51}$Cr-EDTA (clearance) GFR to evaluate the influence of each covariate using nonlinear mixed effects model in 62 oncology patients receiving targeted dosing of carboplatin and validated in an additional 38 patients (49).

The Wright formula estimates of GFR were less biased (mean prediction error $\approx$–3%) and more precise (mean absolute prediction error $\approx$12%) than Jelliffe (–15% and 19%, respectively) or Cockcroft and Gault (–8% and 16%, respectively) estimates.

An example of a dose-determining formula that is on the basis of GFR is the Calvert formula. This formula uses the rate of drug elimination (clearance) and overall systemic drug plasma concentration over time (AUC) to prevent drug toxicity. This formula uses GFR as the measurement of clearance to achieve a target AUC. This approach has been well documented for carboplatin dosing, especially in patients with ovarian or seminoma cancer, whereby a target AUC of 4–6 mg/ml per minute was determined to be the most appropriate therapeutic range. Importantly, increasing the AUC above this range increases the risk of myelotoxicity without improving drug efficacy, and doses below this range can result in higher relapse rates (67,68). The National Comprehensive Cancer Network recommends using the Calvert calculation for carboplatin dosing on the basis of specific AUC targets (such as 4–6 mg/ml per minute). However, taken together, the cancer-specific equations are inferior in performance to the conventional aforementioned equations, such as the CKD-EPI equation, and have not gained wide acceptance or use.

Use of These Measures in Drug Dosing of Chemotherapeutic Drugs
Given the limitations of both measured GFR and eGFR as well as their specific issues in the patient with cancer, how might we incorporate such methods into determining dosing of chemotherapy? In the cancer and noncancer populations, the CKD-EPI equation has proven to have superior performance over other GFR estimating equations and should be recommended as the more accurate estimating equation (57,69).

In addition, both oncologists and nephrologists need to determine the degree of error that is acceptable in the assessment of GFR for clinical decision making for the patient with cancer. If even a moderate degree of error is unacceptable as in the case of carboplatin dosing, then a combination of filtration markers with cystatin C and creatinine should be encouraged together with a measure of GFR, typically with using plasma clearance of iohexol or newer methodologies (see below). Furthermore, repeated assessments of both measured GFR and eGFR should be considered, especially in patients with changes in body mass and composition that can occur with cancer or in the determination of nephrotoxicity. Repeat assessments of both measured GFR and eGFR were highlighted in a recent paper by Rowe et al. (70) and demonstrated that biologic variability is larger for measured GFR than eGFR but also exists for eGFR.

Consider the following scenario in a 62-year-old white woman with ovarian cancer who weighs 62 kg, and her height is 167.6 cm. She is being considered for chemotherapy with carboplatin (Table 2). Her serum creatinine was 1.1 mg/dl, and serum cystatin C was 1.2 mg/L. eGFRcr was 64 ml/min per 1.73 m², eGFRcys was 47 ml/min per 1.73 m², and eGFRcr-cys was 56 ml/min per 1.73 m², all determined by the CKD-EPI equation. This wide variation in eGFR may be explained by inherent errors with the use of creatinine or cystatin C as described above and in Table 2. In this scenario, a more accurate assessment of kidney function was needed, and measured GFR using plasma clearance of iohexol was found to be 49 ml/min.

Real-Time GFR Assessment
The ability to directly measure GFR at the point of care with a rapid, accurate, and reproducible methodology is clearly needed. This ability would allow for adjustment of drug dosing on the basis of accurate assessment of measured GFR that removes many of the problems associated with other measures of GFR previously discussed. In addition, nephrotoxicity can be detected early and even before changes in serum creatinine become manifest. There are
now two methodologies in development that allow for direct quantitative GFR measurement.

The first technology uses a novel exogenous biomarker consisting of a 150-kD rhodamine derivative (which is confined to the vascular space) and a smaller, 5-kD fluorescein carboxymethylated dextran (rapidly filtered by the kidney). Together, these compounds form a visible fluorescent injectate, and concentrations of both compounds can be rapidly measured in plasma using a fluorimeter (71). After a bolus injection of these compounds, the measurement of fluorescence intensity decay can be used to measure kidney function (72,73). In addition, the use of the larger rhodamine derivative, which is retained in the vascular space, allows for determination of volume status. Three low-volume (<1-ml) blood samples are taken over 120 minutes, with the first sample, at 15 minutes, allowing for determination of volume status. In a recent study, this technique showed close linear correlation with iohexol-based measured GFR measurements, including in patients with normal GFR and stages 3 and 4 CKD (71) (Figure 1).

The second technology is a transdermal GFR measurement system (Figure 2) (74). With this methodology, a small light sensor is placed on the patient’s skin, and a biocompatible tracer is administered. The fluorescent tracer (MB-102 or relmapirazin) is removed from the blood exclusively by GFR, and measured fluorescence decreases over time as the substance is cleared by the kidney through GFR. The removal rate is dependent on GFR, and the measured fluorescence time-
dependent curve is converted to a measured GFR using algorithms embedded in the device monitor. Both of these methods would allow for a new paradigm of care where patients might be expected to get measured GFR levels just prior to drug dosing. The measured GFR would be used to adjust the dose of chemotherapy to ensure maximal efficacy and minimal toxicity. In addition, measured GFR could be measured at various time intervals postdrug infusion to detect toxicity and potentially alter treatment plans (for instance, early detection of drug nephrotoxicity may lead to postponing administration of radiocontrast agents or other nephrotoxic agents). Thus, measured GFR allows for both precision and personalized medical care with the hope for better outcomes.

Summary

Effective therapy use of chemotherapeutic agents that have some degree of kidney clearance requires an understanding of kidney function that is typically determined by measurement of eGFR through a regression formula. However, clinicians and pharmacists need to be vigilant in understanding the limitations of this approach and supplement eGFR with more detailed and direct measurement of GFR when needed. These measurements should be taken repeatedly, especially if the patient may not be in a steady-state situation. Newer, real-time measurements of GFR may dramatically improve our ability to more precisely dose chemotherapy, detect early signs of injury, and improve outcomes.

Author Contributions

B. McMahon and M. Rosner wrote the original draft and reviewed and edited the manuscript; M. Rosner conceptualized the study and was responsible for investigation and methodology.

Disclosures

B. McMahon reports other from Sentien Biotechnology, a stem cell research company, outside the submitted work. M. Rosner reports personal fees from Baxter and personal fees from the American Society of Nephrology outside the submitted work.

References


75. Dorshow RB, Bugaj JE: Next tier in vitro and in vivo nonclinical studies further elucidating the safety and toxicity profile of MB-102, a novel fluorescent tracer agent for measurement of glomerular filtration rate. *Regul Toxicol Pharmacol* 107: 104417, 2019
