Drug Dosing and GFR Measurement in Cancer Patients with Kidney Disease

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Bio

- Mitchell H. Rosner, MD, is a nephrologist with a clinical focus on fluid and electrolyte disorders, acute kidney injury, peritoneal dialysis and polycystic kidney disease (PKD). Dr. Rosner is a Principal Investigator on several trials studying novel compounds for the treatment of PKD and leads a regional PKD clinical center. He has published over 150 peer-reviewed journal articles and 7 books. Dr. Rosner serves as the editor-at-large for the Clinical Journal of the American Society of Nephrology and Co-Director for the American Society of Nephrology Kidney Week 2019. He is also the recipient of the 2019 Robert Narins Award from the American Society of Nephrology, recognizing his contributions to the field.

- Dr. Rosner is the Henry Mulholland Professor of Medicine and Chair of the University of Virginia Department of Medicine. He is board-certified in both internal medicine and nephrology.
Disclosures

• M. Rosner reports consulting fees from Baxter and personal fees from the American Society of Nephrology
Objectives

• Understand the importance of measuring kidney function for chemotherapeutic drug dosing
• Describe the various methodologies that use exogenous and endogenous markers to determine kidney function
• Understand the pitfalls of using regression equations in the measurement of kidney function
• Recognize novel methodologies to determine kidney function and aid drug dosing in CKD patients with cancer
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.
• While drug elimination from the kidneys may involve both glomerular filtration and tubular secretion, the best measure of kidney function is GFR, which has generally been accepted as a measure of functioning kidney mass
• Measures to directly and indirectly measure GFR have been well validated, and there is extensive experience with their operational characteristics
Drugs of Concern

• 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.

• Carboplatin is unique among chemotherapeutic agents in that its dosing is largely on the basis of determination of eGFR

• In some cases, drug levels can be measured and dosing adjusted to reach therapeutic levels (such as with methotrexate and cyclophosphamide), in other cases this is more difficult or is not feasible
Personalized Dosing Strategies

- Efficacy and safety of personalized cyclophosphamide (CY) dosing in 50 patients receiving CY with total body irradiation (TBI). Participants received CY with subsequent therapeutic drug monitoring to personalize the second CY dose to a target area under the curve.
- Patients receiving personalized CY dosing had significantly lower post-conditioning peak total serum bilirubin (p=0.03); a 38% reduction in the hazard of acute kidney injury (p=0.03); and similar non-relapse and overall survival (p=0.70 and 0.63, respectively) despite lower doses of CY in most patients.

Abnormal Kidney Function in Common in Patients with Cancer and May Be Unrecognized

• Although it is generally true that a rise in serum in creatinine generally reflects a fall in GFR, serum creatinine levels only roughly track with GFR due to factors, such as age, muscle mass, meat intake, and race.

• 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.

• As an example of this, Launay-Vacher and colleagues 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 had a GFR > 90 ml/min per 1.73 m² at the time of therapy initiation.

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https://doi.org/10.34067/KID.0000952019
GFR in Patients with Cancer

Survival and GFR in Cancer Patients- IRMA-2

The Effect of Impaired GFR on Chemotherapeutic Pharmacokinetics and Drug Toxicity

• 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.
  • 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.

• In addition, the volume of distribution of a drug is significantly affected by serum protein binding. In patients with hypo-albuminemia (from nephrotic syndrome or poor nutritional status), the free fraction of some drugs may be increased, leading to altered kinetics and actions.

• In those patients with significantly impaired kidney function, uremic toxins can compete with drugs for plasma protein-binding sites, also leading to altered pharmacokinetics.

Kidney Function Must be Assessed

• 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

Failure to Recognize Impaired Kidney Function

• 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.

• 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.

• The use of kidney function measurements and appropriate dose modifications can improve outcomes.

Use of Exogenous Markers to Determine GFR

- Time consuming, labor intensive, costly and not routinely available
- There are several exogenous markers that can be used for determination of GFR:
  - Inulin
  - Radionuclide agents include $^{125}\text{I}$-iothalamate and $^{51}\text{Cr}$-EDTA (detected by plasma levels) or $^{99}\text{Tc}$mercaptoacetyltriglycine and $^{99}\text{Tc}$diethyl triamine penta-acetic acid (detected by g-counter)
  - Radiocontrast markers include iohexol and diatrizoate meglumine, which are often determined by high-performance liquid chromatography
- 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.

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Cystatin C

• 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.

• Thus, cystatin C measurements alone are not appropriate for measurement of kidney function or for detection of nephrotoxicity.

Pract Lab Med 8: 95–104, 2017
Regression Equations

- Given their ease of use and extensive validation studies, regression equations (eGFR measurements, creatinine clearance estimations, and cancer-specific equations) are most commonly used.

- These GFR estimating equations allow estimation of GFR (eGFR) with the use of endogenous filtration markers, such as serum creatinine and serum cystatin C, and they are accepted per current clinical practice guidelines.

- 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.

- 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.
BSA Indexing or Not?

- 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.
- 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.
- More data is needed

Cancer-Specific Regression Equations

- Examples include the Martin and Wright equations but likely not as accurate as CKD-EPI equation

- 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).
  - 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.

  J Cancer 84: 452–459, 2001
International Consensus Guideline for Anticancer Drug Dosing in Kidney Dysfunction (ADDIKD)

Public consultation draft
April 2022

eviQ

Presented for public comment in April 2022
New International Guideline

• The International Consensus Guideline on Anticancer Drug Dosing in Kidney Dysfunction (ADDIKD) has been developed in accordance with international best practice using a framework that aligns with the 2016 National Health and Medical Research Council Standards for Guidelines.

• ADDIKD provides a standardized approach to anticancer drug dosing in kidney dysfunction, founded on evidence-based literature and formulated by an expert clinical working group, addressing the paucity in data by providing consensus recommendations.
Recommendations

• We recommend the use of estimated glomerular filtration rate calculated via the Chronic Kidney Disease – Epidemiology Collaboration (eGFR CKD-EPI) equation to guide the assessment of kidney function, except where directly measured glomerular filtration rate (mGFR) is clinically necessary.

• This is **without** the race coefficient.

• eGFR CKD-EPI is indexed to a standardized body surface area (BSA) of 1.73 m² to enable comparison of kidney function between individuals with different body sizes with the assumption that BSA is a reliable indicator of kidney size.

• The applicability of the BSA reference value of 1.73 m² to the larger-sized contemporary population has been questioned.
Recommendations

• Use eGFR CKD-EPI results obtained as close as possible to the time of administering the anticancer drug(s) to ensure it is a reflective estimation of the patient’s steady state kidney function.

• Kidney function assessment is advised at the beginning of anticancer drug treatment (first cycle) and should be considered prior to subsequent cycles of anticancer drug treatment.

• Consider performing a second eGFR CKD-EPI prior to initiating anticancer drug treatment if:
  • the clinical state of the patient has changed since the most recent eGFR CKD-EPI result, or there is a suspicion of declining kidney function
  • the last reported eGFR CKD-EPI < 60 mL/min/1.73 m2 and the dose of the intended anticancer drug(s) is guided by kidney function.
Recommendations

- Clinical situations where calculating eGFR CKD-EPI may not be reliable include (but are not limited to):
  - Acute kidney injury
  - Fluid overload or volume depletion
  - Obesity (Studies have shown eGFR CKD-EPI to underestimate kidney function in obese patients)
  - Sarcopenia
  - Exceptional dietary intake (e.g., vegetarian diet, high protein diet, creatine supplements) or recent consumption of cooked meat
  - High muscle mass
  - Advanced liver disease
  - Drugs interfering with creatinine secretion
  - Pregnancy
Recommendations

• Directly measured GFR is preferred to guide the initial dosing for a select group of anticancer drugs including, but not limited to, carboplatin, cisplatin, and methotrexate (≥ 500 mg/m²).
• Direct measurement may be through the use of any well validated and locally available methodology.
The use of kidney function to inform the initial dosing is:

- **recommended** for bleomycin, capecitabine, carboplatin, cisplatin, cyclophosphamide, etoposide (including etoposide phosphate), fludarabine, lenalidomide, methotrexate, raltitrexed, and topotecan.

- **suggested** for high-dose cytarabine (≥ 1000 mg/m²), dacarbazine, daunorubicin (including liposomal daunorubicin), fluorouracil, idarubicin, ifosfamide, irinotecan, melphalan, mercaptopurine, mitomycin, oxaliplatin, pemetrexed, procarbazine and vinflunine.

- **recommended against**, but kidney function may inform the monitoring of adverse events and the selection of an alternative treatment protocol, for obinutuzumab, and venetoclax.

- **recommended against**, but kidney function may inform the monitoring of adverse events, for bendamustine, cabazitaxel, chlorambucil, gemcitabine, paclitaxel, and thalidomide.

- **suggested against**, but kidney function may inform the monitoring of adverse events, for azacitidine, bevacizumab, bortezomib, dactinomycin, **pegylated liposomal** doxorubicin, everolimus, nab-paclitaxel, temozolomide, and thiotepa.

- **recommended against** for cetuximab, dabrafenib, docetaxel, doxorubicin, epirubicin, nivolumab, panitumumab, pembrolizumab, vinblastine, vincristine, vindesine, and vinorelbine.

- **suggested against** for low-dose cytarabine (< 1000 mg/m²), durvalumab, pertuzumab, rituximab, trastuzumab, and trastuzumab emtansine.
An initial dose reduction or a clinically appropriate alternative treatment protocol, under specific conditions, is:

- **recommended for eGFR < 60 mL/min/1.73 m²** in capecitabine, cisplatin, fludarabine, lenalidomide, methotrexate, raltitrexed, and topotecan.
- **suggested for eGFR < 60 mL/min/1.73 m²** in high-dose cytarabine (≥ 1000 mg/m²), fluorouracil, melphalan, mercaptopurine, and vinflunine.
- **recommended for eGFR < 45 mL/min/1.73 m²** in bleomycin and etoposide (including etoposide phosphate).
- **suggested for eGFR < 45 mL/min/1.73 m²** in ifosfamide, pemetrexed, and procarbazine.
- **suggested for eGFR < 30 mL/min/1.73 m²** in cyclophosphamide, dacarbazine, daunorubicin (including liposomal daunorubicin), idarubicin, irinotecan, mitomycin, and oxaliplatin.
- **suggested against for < 60 mL/min/1.73 m²** azacitidine, bendamustine, bortezomib, low-dose cytarabine (< 1000 mg/m²), dactinomycin, pegylated liposomal doxorubicin, gemcitabine, nab-paclitaxel, and temozolomide.
- **suggested against for eGFR < 60 mL/min/1.73 m²** in carboplatin, but use the Calvert formula with a target area under the curve for dosing instead.
62-year-old white woman with ovarian cancer who weighs 62 kg, and he height is 167.6 cm.

- She is being considered for chemotherapy with carboplatin.
- 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.
- 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.
### ANTICANCER DRUG DOSE RECOMMENDATIONS

<table>
<thead>
<tr>
<th>eGFR (mL/min/1.73 m²)</th>
<th>Dose</th>
<th>Comment</th>
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<tbody>
<tr>
<td>≥ 60</td>
<td>full dose</td>
<td>Increased risk of adverse events.</td>
</tr>
<tr>
<td>45–59</td>
<td>full dose</td>
<td>Consider a 25% dose reduction in patients with either:</td>
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<td></td>
<td></td>
<td>- non-curative treatment intent</td>
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<td></td>
<td></td>
<td>- concomitant nephrotoxic drug exposure</td>
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<td>- a poor performance status</td>
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<td></td>
<td></td>
<td>In all other patients, consider a clinically appropriate alternative treatment protocol</td>
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<tr>
<td></td>
<td></td>
<td>Increased risk of adverse events.</td>
</tr>
<tr>
<td>30–44</td>
<td>reduce by 25% or alternative protocol</td>
<td>Not recommended – use a clinically appropriate alternative treatment protocol</td>
</tr>
<tr>
<td>15–29</td>
<td>AVOID</td>
<td>Consult a multidisciplinary team consisting of oncology/haematology with nephrology and/or clinical pharmacology for the management of dosing.</td>
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<td>≤ 15 (without KRT)</td>
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**Footnotes with drug specific practice points**
Newer Methodologies
Newer Methodologies

- Patented fluorescent tracer agent

- Device
  - Transdermal fluorescence detection sensor
    - LED light source
    - Photodetector
  - Display monitor
    - Data acquisition software
    - GFR calculation software

The fluorescent tracer (MB-102 or remapirazin) is removed from the blood exclusively by GFR, and measured fluorescence decreases over time as the substance is cleared by the kidney (75). The removal rate is dependent on GFR.
Summary

• Patients with CKD develop cancer and many chemotherapeutic agents are removed from the body through renal excretion

• Measurement or accurate estimation of GFR is critical in ensuring correct dosing to minimize toxicity and maximize response

• The CKD-EPI equation may be used (without race coefficient) but for certain drugs, a measured GFR should be obtained

• Patients receiving nephrotoxic medications should have their GFR closely monitored

• Newer technologies offer promise of near real-time and accurate GFR assessment