BC Cancer Clinical Pharmacy Guide

Renal Function Laboratory Tests

Contents

Introduction

The kidneys are responsible for various important body functions including removal of waste material from the blood (creatinine, urea, uric acid), regulating electrolytes, extracellular fluid volume and blood pressure, and secreting hormones involved in red blood cell production (erythropoietin) and bone metabolism (calcitriol, vitamin D3). Cancer drugs that are cleared renally can require dose adjustments for patients with renal dysfunction. Some cancer drugs are nephrotoxic (cisplatin), and the cancer treatment can cause kidney damage. Additionally, the disease processes of cancers like kidney, liver or multiple myeloma may also cause kidney damage. Clinical manifestations range from electrolyte disorders and proteinuria to more severe kidney injury resulting in permanent loss of renal function or kidney failure requiring external filtration (hemodialysis, peritoneal dialysis) or kidney transplant.

Estimation of renal function should be as accurate as possible when treating a patient with drugs that are renally eliminated or potentially nephrotoxic. A renal function assessment should be done prior to the start of cancer drug treatment to ensure that the patient has adequate renal function to eliminate renally cleared drugs. This baseline value also serves as the point of reference to which future measurements are compared. Declining renal function may suggest the need for clinical interventions, such as dose modifications, to prevent accumulation of renally eliminated drugs and/or to manage nephrotoxicity. As with all other laboratory tests, it is important to observe the trend rather than a single, isolated measurement.

Table 2: Examples of Renally Eliminated Cancer Drugs

arsenic	etoposide	methotrexate
bleomycin	fludarabine	mitomycin
capecitabine	gemcitabine	oxaliplatin
carboplatin	ifosfamide	pemetrexed
carmustine	lenalidomide	raltitrexed
cisplatin	lomustine	temozolomide
cladribine	melphalan	topotecan
cyclophosphamide		

There is no serum lab test available to quantitatively measure renal function. Instead, the serum tests available assess the concentration of specific proteins that are cleared by the kidneys as markers to estimate renal function:

- **Serum creatinine (SCr)** - a product of muscle breakdown that is filtered by the glomerulus in the kidneys
- **Blood urea nitrogen (BUN, urea nitrogen, or urea)** - a waste product of protein and amino acid metabolism that accumulates when renal function is reduced

SCr and BUN do not completely represent the renal function status because they can be affected by processes occurring outside the kidneys (e.g., dehydration or the liver's production of urea).

The only method to accurately assess kidney function is to measure the Glomerular Filtration Rate (GFR) by nuclear renogram.

Glomerular Filtration Rate (GFR)

Glomerular filtration rate (GFR) is the rate that substances, like creatinine, are filtered by the glomerulus. GFR can be used as a proxy measure of renal function.

It is most accurately measured with a nuclear renogram (measured GFR). However, as a nuclear renogram involves injection of a renally excreted radioisotope (e.g., ^{99m}Tc-DTPA) and serial imaging of the kidney obtained with a gamma camera to generate a time-activity curve (i.e., renogram), it is not used routinely.

Serum creatinine (SCr) can be used to calculate a creatinine clearance (CrCl) to approximate the GFR. Some limitations include:

- GFR estimates filtration by the glomerulus in the kidneys. A calculated CrCl overestimates GFR because serum creatinine is cleared by glomerular filtration and tubular secretion. A calculated CrCl provides a reasonable estimate of GFR for healthy patients with minimal tubular secretion; it is less accurate (overestimated) for patients with chronic kidney disease with increased tubular secretion.
- Patient weight is a source of inaccuracy in calculating CrCl, because actual weight does not account for how much of the weight is lean tissue, which is where creatinine is produced. The GFR may be underestimated in patients with increased muscle mass and overestimated in patients who are obese or edematous.
- GFR may be underestimated (falsely low) for non-renal reasons such as:
    - dehydration resulting in increased serum creatinine levels

  - high protein diet or creatine supplementation (possible transient serum creatinine increase within 2 hours after a high protein meal)
  - high muscle mass
  - muscle breakdown (e.g., after heavy exercise, myositis)
- GFR may be overestimated (falsely high) for non-renal reasons such as:
  - drinking lots of water prior to blood test resulting in decreased serum creatinine levels
  - low protein diet (vegetarian)
  - low muscle mass (elderly, amputee or malnourished patients)
  - muscle wasting (late-stage muscular dystrophy, myasthenia gravis)
- Timing of blood samples may affect the GFR calculation because of diurnal variations in serum creatinine.
- Sudden changes in renal function, such as acute renal failure in hospitalized patients, will not be immediately reflected in the measured SCr.

The accuracy of using a calculated CrCl to estimate GFR is also debated for patients with other conditions such as chronic renal insufficiency, diabetes mellitus, elevated albumin levels, and serum creatinine concentrations less than 10 micromol/L. See the *Lab Test Interpretation Table*, located below this document on the Clinical Pharmacy Guide webpage, for examples of normal values and interpretation tips.

Cockcroft-Gault Calculation of Creatinine Clearance

In 1976, Cockcroft and Gault proposed a simple equation that estimated creatinine clearance using the patient's creatinine, age and weight. BC Cancer uses the following modified Cockcroft-Gault equation to calculate creatinine clearance. This calculation is built into BC Cancer electronic order dose calculators.

Cockcroft-Gault equation:

$$\text{Calculated creatinine clearance (mL/min)} = \frac{N \times (140 - \text{age}) \times \text{weight (kg)}}{\text{Serum creatinine (micromol/L)}}$$

Where:
N = 1.04 for females
N = 1.23 for males

Laboratory Reported Calculation of Creatinine Clearance

Laboratories also calculate GFR, reported as an estimated glomerular filtration rate (eGFR) when serum creatinine is ordered. A number of recognized formulae have been utilized for this purpose, including the Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations. BC labs now use the CKD-EPI equation.

Protocols suggest using the same method of calculating GFR for consistency throughout the treatment course (i.e., if a lab reported GFR estimate was used initially, it should be used for dosing in all subsequent cycles instead of the Cockcroft-Gault estimate). Typically, protocols suggest using calculated CrCl for renal dose adjustments, however, protocols containing lenalidomide do mention using eGFR for lenalidomide renal dose adjustments.BUN to Creatinine Ratio (BUN:SCr)

BUN to Creatinine Ratio (BUN:SCr)

Comparing the ratio of Blood Urea Nitrogen (BUN or urea) to Serum Creatinine (SCr) can also help provide clues about disease processes that may be the cause of abnormal test results. Like SCr, BUN levels vary with hydration status, protein intake and renal excretion. Unlike SCr, BUN levels can also vary with hepatic urea synthesis, gastrointestinal bleeding, protein catabolism, urine flow rate, fever, infection, glucocorticoid use or renal reabsorption.

The BUN:SCr ratio is calculated based on the conventional American units (mg/dL) for both BUN and SCr, where BUN is divided by SCr. These values are reported in SI units in Canada. The conversion factors for these values are:

BUN mg/dL = BUN mmol/L x 2.8

SCr mg/dL = SCr micromol/L x 0.01131

MediCalc is a website that provides a calculator for determining the BUN to SCr ratio directly from SI or conventional units.

Elevated (BUN:SCr > 15:1)

A higher than usual ratio suggests an abnormal process outside the kidneys that interferes with normal kidney function. This can occur either at the point where blood is delivered to the kidney for filtering (prerenal) or at the point where urine leaves the kidneys (postrenal). Although an elevated ratio is considered to be > 15:1, prerenal and sometimes postrenal disease causes ratios > 20:1. However, a ratio > 20:1 is not clinically significant if both the BUN and SCr are within normal limits. Certain medications such as tetracyclines and corticosteroids can also cause a transient increase in BUN.

Prerenal Causes

Prerenal causes of an increased BUN:SCr ratio include decreased renal blood flow (perfusion). Delivery of blood to the kidneys for filtering may be impaired by intravascular volume depletion from dehydration, blood loss, shock or heart failure. The increase in BUN relative to SCr is due to the passive reabsorption of urea that follows increased sodium and water reabsorption. The subsequent elevation in BUN-to-creatinine ratio can be > 20:1, indicating decreased renal perfusion as the cause. In patients receiving cancer drugs, common prerenal causes of kidney impairment include vomiting, diarrhea and fever.

Postrenal Causes

Postrenal causes of elevated BUN:SCr ratio occur when movement of urine from the kidneys is obstructed, which is often due to an enlarged prostate from prostatitis or cancer (e.g., prostate, bladder, uterine, or cervical). Low urine flow rates allow more time for urea to be reabsorbed. Other potential causes of urinary tract obstruction include kidney stones.

Non-renal Causes

An increased ratio may be the result of increased urea production from gastrointestinal bleeding, tissue breakdown, or corticosteroid administration.

Loss of muscle mass in elderly or chronically ill patients can decrease creatinine production which increases the BUN:SCr ratio. This is a chronic problem and does not explain an acute increase.

Normal (BUN:SCr 10:1 to 15:1)

Disease process within the kidneys (intrarenal or intrinsic causes) usually lead to a normal ratio as both BUN and SCr levels may increase with reduced renal filtration capacity.

Possible causes of acute kidney injury in patients with cancer include multiple myeloma light chains (causing tubular injury and cast formation), tumour lysis syndrome (released intracellular contents causing tubular injury and obstruction), kidney infiltration by lymphoma or acute leukemia, and nephrotoxic drugs via different mechanisms (e.g., renal vascular and tubular injury by cisplatin or intratubular crystallization by high-dose methotrexate).

Other examples of intrarenal causes include glomerulonephritis, renal tubular disease, pyelonephritis, severe hypertension, diabetes, and arteriosclerosis.

A normal ratio can occur in prerenal disease if it is accompanied with decreased urea production as a result of reduced protein intake or liver disease.

Reduced (BUN:SCr < 10:1)

A lower than usual ratio (<10:1) usually suggests decreased urea production as a result of reduced protein intake or liver disease.

Urinalysis for Protein

Urine tests can also be used to assess renal function. Protein is a large molecule and normally very little protein is filtered into the urine. Persistently increased levels of protein in the urine can suggest kidney damage.

Certain protocols such as CNBEV or GILEN require monitoring urine dipstick analysis or laboratory urinalysis for protein as the anti-vascular endothelial growth factor drugs (bevacizumab) or anti-vascular endothelial growth factor receptor drugs (lenvatinib) involved can cause proteinuria or nephrotic syndrome. If enough protein is detected in the single urine test, a 24 hour urine collection for protein may be required to make dose adjustments prior to the next treatment cycle and to ensure treatment can continue.

Carboplatin Dosing

Assessing renal function plays an important role in determining the optimal dose for carboplatin. The BC Cancer protocols base carboplatin doses on patient-specific renal function, while most other cytotoxic cancer drugs use body surface area to determine dosage. Examples of carboplatin-containing protocols include BRAJDCARBT, GOENDCAT and GOOVCARB.

Although carboplatin can be dosed based on BSA, there is poor correlation between BSA and the risk of developing thrombocytopenia; however, there is a strong correlation between total body clearance of carboplatin and GFR, as this drug is mainly eliminated renally.

It has also been shown that the percentage of reduction in platelet count is proportional to the area under the curve (AUC) for carboplatin plasma concentration versus time. In 1989, Calvert and his colleagues proposed a simple equation for optimizing carboplatin dosing based on the AUC, patient-specific GFR, and non-renal elimination. The formula is as follows:

$$\text{Carboplatin Dose} = \text{AUC} \times (\text{GFR} + 25)$$

Where:
Carboplatin Dose = total carboplatin dose in mg
AUC = desired AUC in mg/mL × min
GFR = glomerular filtration rate*
25 = average non-renal clearance for adults

*GFR is capped at 125 mL/min if it was estimated from a serum creatinine level. The actual GFR can be used if it was measured by nuclear renogram (see GFR and Carboplatin Dosing below)

The AUC depends on the treatment history of the patient. Patients who are chemotherapy-naive may start at an AUC as high as 7 per cycle every 3 to 4 weeks; while heavily pretreated patients may start at an AUC of 5, as previous exposure to myelosuppressive drugs increases the risk of developing thrombocytopenia by 17%. In order to increase the margin of safety, protocol summaries developed at BC Cancer start with an AUC of 6. Patients with extensive prior radiation therapy, significant cytopenia with prior therapy, or age greater than 80 are usually started with an AUC of 5. Protocols that use weekly carboplatin during radiation have a reduced AUC dose of 2 (e.g., GIENACTRT). Clinical judgment also plays a role in determining the AUC for a treatment course of carboplatin.

Thrombocytopenia is the major dose-limiting side effect of carboplatin, and a platelet count is routinely performed at the nadir between initial cycles of carboplatin or as needed following dose adjustments. If there is a decline in platelet count, the carboplatin dose is reduced for subsequent treatment cycles.

Drug tolerability in patients receiving carboplatin is assessed by monitoring the platelet count and serum creatinine. Even when the initial dose is calculated based on a renogram estimate of GFR, serum creatinine is monitored to ensure that renal function is stable throughout the course of treatment. If the serum creatinine increases, this may indicate a decline in renal function. Consult the protocol and general references to determine whether a dose reduction is required. The platelet count is also monitored at the nadir between cycles of carboplatin, and at the beginning of each cycle. The nadir is usually observed at week 3 of a 4 week cycle between doses. Protocols containing carboplatin usually include dose modifications based on the nadir platelet count.

GFR and Carboplatin Dosing

As outlined in the GFR section above, a measured GFR (e.g. nuclear renogram) can be ordered if an accurate measure of GFR is required. Typically, the Cockcroft-Gault calculated estimate of GFR (calculated CrCl) or the lab reported estimate of GFR (eGFR) is used to calculate carboplatin dosing. However, if a nuclear renogram was available, this measured clearance would take precedence. Some protocols using carboplatin suggest that measured GFR is preferred in circumstances of co-morbidity that could affect renal function (e.g., third-space fluid accumulations, hypoproteinemia, potentially inadequate fluid intake, etc.).

In BC Cancer protocols, the estimated GFR, reported by the lab or calculated using the Cockcroft-Gault equation, is usually capped at 125 mL/min when it is used to calculate an initial carboplatin dose, e.g., LUAJPC. Some protocols ask that GFR and carboplatin dose be recalculated if the serum creatinine increases or decreases by 20% or more from the level used to calculate the current dose, or rises above the ULN, e.g., GOOVPLDC. If the recalculated carboplatin dose changes by 5% or more, consult the prescriber to discuss updating the carboplatin dose.

Note: it is recommended that the same method of GFR estimation be used for calculation of doses throughout a treatment course. If a lab reported GFR is used initially, dosing for all subsequent cycles should also be based on the eGFR, and not the Cockcroft-Gault estimate. BC labs use the Chronic Kidney Disease Epidemiology collaboration formula (CKD EPI) to estimate eGFR. Some clinical trials may require

calculation of renal function using the older Modification of Diet in Renal Disease (MDRD) formula. This is an exception and must be followed as per the clinical trial requirements.