RENAL FUNCTION IN THE ELDERLY

Christopher Steer ■ Border Medical Oncology, Wodonga, Victoria
Email: csteer@bordermedonc.com.au

Abstract

Although it is generally accepted that renal function declines with increasing age, this should not be assumed in all cases. The estimation of renal function on an individual patient basis is therefore required. This is especially important in patients who are prescribed potentially nephrotoxic agents or chemotherapy which is renally excreted. The measurement of serum creatinine alone is inadequate for this task. The various ways in which more accurate measures of renal function can be estimated are discussed. The most common method in clinical practice is the estimation of creatinine clearance using the Cockcroft and Gault formula. The International Society of Geriatric Oncology has produced clinical practice recommendations on the estimation of renal function in the elderly and on chemotherapy dosing in patients with impaired renal function. These practical recommendations can be easily adapted into everyday clinical practice.

It is generally accepted that renal function declines in the elderly patient population. This is due to the presence of co-morbidity and a decline in renal reserve. Care must be taken not to assume that a reduced Glomerular Filtration Rate (GFR) is a normal part of ageing. Studies such as the Baltimore Longitudinal Study on Ageing suggest that the principle cause of the decline seen in the general elderly population is hypertension. This debate aside, most studies show a decline in GFR with increasing age (Figure 1).

The impact of physiological changes associated with age on the pharmacokinetic and pharmacodynamic properties of drugs can be considerable, particularly for the renal elimination of drugs and metabolites. This is especially so for those drugs that are principally renally excreted and/or are nephrotoxic. These drugs typically have a narrow therapeutic range and dose adjustment may be required to avoid drug accumulation and toxicity.

Assessment of patients’ renal function is therefore vital prior to the use of renally excreted or potentially nephrotoxic drugs. Reliance on the serum creatinine concentration is inappropriate in the elderly patient population and may lead to dosing errors and avoidable toxicity. More accurate methods of assessment of renal function are readily available.

Figure 1: Relationship of estimated glomerular filtration rate (eGFR) as derived by the MDRD formula to age

* At: median (50% of subjects have eGFR above this line); B: 80% of subjects have eGFR above this line; C: 97.5% of subjects have eGFR above this line. These reference lines are derived from over 300,000 presentations to a large private pathology service, with exclusion of creatinine results lying outside a Gaussian distribution for each age decade (personal communication, Ken Sikaris, Chemical Pathologist, Melbourne Pathology Service, VIC).


Population ageing – global scope of the problem

A recent United Nations report on the global phenomenon of the ageing population produced four major findings; population ageing is unprecedented, global, enduring and profound, having implications for all facets of human life. As long as old age mortality continues to decline and fertility remains low, the proportion of older people will continue to increase.

Globally, the population of older people is itself ageing. Among those aged 60 years or over, the fastest growing population is that of the oldest-old, that is, those aged 80 years or over. Today, people aged 80 years or over account for about one in every eight older people (60 or over). By 2050, this ratio is expected to increase to approximately two in every 10 older people.

In 2000, the population aged 60 years or over numbered 600 million, triple the number in 1950. In 2006, the number had surpassed 700 million. By 2050, two billion older people are projected to be alive, implying that their number will once again triple over a span of 50 years.

The median age of patients in Australia at the first diagnosis of cancer is 67 years. As the population ages we expect the burden of cancer to be more common, especially in the elderly patient population.

Terminology

**Stage Description GFR (ml/min/1.73m²)**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>GFR (ml/min/1.73m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kidney damage with normal or increased GFR</td>
<td>&gt;90</td>
</tr>
<tr>
<td>2</td>
<td>Kidney damage with mild decrease in GFR</td>
<td>60-89</td>
</tr>
<tr>
<td>3</td>
<td>Moderate decrease in GFR</td>
<td>30-59</td>
</tr>
<tr>
<td>4</td>
<td>Severe decrease in GFR</td>
<td>15-29</td>
</tr>
<tr>
<td>5</td>
<td>Kidney failure</td>
<td>&lt;15 (or dialysis)</td>
</tr>
</tbody>
</table>

Chronic kidney disease is defined as either kidney damage or GFR < 60ml/min/1.73 for more than three months.

### Serum creatinine concentration

Serum creatinine concentration is the most commonly used marker of renal function. It is an easily measured parameter, but when used alone does not provide an accurate measure of renal function. Serum creatinine concentration varies with sex, age, muscle mass, drugs and diet. Ingestion of a meal containing cooked meat has been shown to raise serum creatinine concentration by a median value of 20 μmol/L. Serum creatinine is expressed in different units in different countries. In Australia and New Zealand, the use of SI units (μmol/L) is now recommended. In the United States serum creatinine is reported in mg/100ml (mg/dL). The following formula is used to convert from mg/100ml to μmol/L:

\[ SCr(\mu\text{mol/L}) = SCr(\text{mg/100ml}) \times 88.4 \]

Whereas renal function as defined by GFR decreases with age, serum creatinine concentration may not rise accordingly. Elderly patients with normal serum creatinine concentrations may have significant impairment of renal function. Swadko and colleagues investigated the specificity and sensitivity of serum creatinine concentration in the diagnosis of renal failure (GFR < 50ml/min). If a serum creatinine concentration of 150μmol/L was used as a definition of renal failure in a population of 854 patients over the age of 65 years, the sensitivity was 12.6% and specificity 99.1%. The sensitivity of detecting severe renal failure (GFR < 30ml/min) was 45.1%. For this reason it is vital to estimate GFR in elderly patients rather than rely on serum markers alone.

Serum Cystatin C is a serum marker which has the potential to be more accurate in the estimation of GFR than serum creatinine. Despite studies demonstrating increased accuracy, this marker has not been widely accepted, largely due to increased cost.

### Glomerular Filtration Rate

The best estimate of renal function is the GFR. True GFR is measured in ml/min. Standardised GFR is routinely used by clinicians such as nephrologists as a marker of patients' renal function. This is an adjusted figure that assumes an average body surface area of 1.73m². Standardised GFR is reported in ml/min/1.73m².

It is important to note that the standardised GFR should not be used to calculate the dose of renally excreted drugs. An estimate of actual GFR should be used. Conversion from ml/min/1.73m² to ml/min requires knowledge of the patients height and weight. After calculation of body surface area (BSA) the following formula can then be used:

\[ \text{GFR (ml/min) = GFR (ml/min/1.73m²) \times BSA/1.73} \]

### Estimating GFR

The estimation of GFR requires sophisticated testing techniques which are widely available but impractical for routine use. Nuclear medicine isotopic methods are the “gold standard” against which other techniques are measured. The two commonly used methods in clinical practice involve the use of:

- \(^{51}\text{Cr} – \text{EDTA (I}^{51}\text{Cr})\)-ethylenediamine tetraacetic acid
- \(^{99m}\text{Tc} – \text{DTPA (technetium}^{99m}\text{diethyl triamine penta-acetic acid)}

Timed blood samples are taken after delivery of a dose of radioisotope. The concentration of isotope in the sample is then used to determine “true” GFR.

### Creatinine clearance (CrCl)

The creatinine clearance is an estimate of GFR. CrCl can be either measured or calculated.

CrCl can be measured using a 24-hour urine collection however this method is unreliable, labour intensive and is not recommended for routine use.

Alternative techniques to estimate CrCl have been developed based on the serum creatinine concentration. Over 40 formulae have been devised to estimate CrCl. All formulae are based on the patient’s serum creatinine concentration and age. Some also require knowledge of the patient’s height and weight.

### Commonly used formulae

1. **Cockcroft and Gault**

   \[
   \text{CrCl (ml/min) = } \frac{(140 – \text{Age}) \times \text{wt (kg)}}{72 \times \text{SCr(mg/100ml)}}
   \]

   The formula published by Cockcroft and Gault was derived from a population of 249 men in a veterans’ hospital. As no women took part in the study the formula employs an arbitrary correction factor of 0.85 when calculating the CrCl of female patients. The mean age of patients in the dataset was 57 years (range 18-92 years). Twenty nine per cent of the study population were over the age of 70 years. The formula was derived using measured 24 hour creatinine clearance as the “gold standard”.

   The Cockcroft and Gault formula is reported in ml/min and does not require conversion when used to calculate doses of renally excreted drugs such as carboplatin. The published formula uses a SCr value expressed in
measured by the urinary clearance of 125I-iothalamate initially derive the formula, glomerular filtration rate sex in addition to serum creatinine concentration. To
2% of participants had a GFR of >90ml/min/1.73m². The original MDRD formula was derived from 1704 participants with renal disease.17 A modified MDRD formula then is assessed as to their bias and precision in estimating GFR.

The eGFR has not been validated in certain ethnic groups such as the Aboriginal and Torres Strait Islander population. Although it has been recommended to be reported in non-caucasian Australian populations, validation studies are needed to ensure accuracy and precision.

Limitations of formulae to estimate creatinine clearance

All formulae used to estimate creatinine clearance rely on the serum creatinine concentration. All formulae are imprecise in their estimation of GFR. The formulae lack precision and are particularly unreliable in the following circumstances:

1. At the extremes of serum creatinine. In patients with high serum creatinine and with low measured GFR or patients with very low serum creatinine and high GFR.
2. In patients at the extreme of body size (ie. in cachexia, severe malnutrition and obesity).
3. If the serum creatinine is changing rapidly (eg. in intensive care).
4. Formulae may not be validated in specific patient populations (eg. the elderly and different ethnic groups) eg. the MDRD equation was devised in patients with renal disease and care needs to be taken if it’s going to be applied in patients with GFR>90ml/min/1.73m².

As all formulae are inaccurate at the extremes of GFR, it remains appropriate to perform isotopic estimation of GFR in some cases.

How do the formulae compare?

A number of studies have been published in which the various formulae have been compared. Most studies compare the formulae against a “gold standard”, which is usually an isotopic method of estimating GFR. The formulae then are assessed as to their bias and precision in estimating GFR.

The formulae mentioned above have been compared by a number of authors. The literature does not enable us to detect a clear “winner”, however some formulae are more practical and seem to be better in certain situations.

The Cockcroft and Gault formula is the most widely known and the simplest test to perform; it is truly a bedside test of renal function. The Wright formula is slightly more complex, and was devised in patients with
malignancy rather than renal disease. The MDRD cannot be assessed without the aid of a computer due to the need to calculate exponentials. In addition, most online calculators of the MDRD formula do not report a GFR figure >90ml/min/1.73. Despite this, there has been at least one call for the MDRD to be utilised more widely by cancer physicians.\textsuperscript{29} Despite the bias and imprecision of the various formulae, it is much better to use one of them than rely on measurement of the serum creatinine concentration alone. Use of the formulae will require acceptance of some degree of inaccuracy. In some clinical situations, small errors may be acceptable and not lead to clinically relevant adverse outcomes.

**Use of formulae in the elderly patient population**

In medical oncology practice, formulae to estimate creatinine clearance are used principally to estimate GFR (ml/min), to insert into the Calvert equation to then calculate the dose of carboplatin.\textsuperscript{30} Currently this is the only chemotherapeutic drug that is dosed in this fashion. Other drugs (eg. capectabine) require calculation of patients’ renal function and subsequent dose reduction in the event of renal impairment. Due to the decline in GFR seen with increasing age, often seen despite a serum creatinine concentration in the normal range, the estimation of creatinine clearance is essential.\textsuperscript{31}

The Cockcroft and Gault, Wright and Jelliffe formulae have been compared in a population of 225 elderly patients with cancer.\textsuperscript{21} In a retrospective analysis, the Wright formula was found to be the least biased and most precise in patients over the age of 70 years. This advantage was seen in the patients with “normal” renal function (GFR between 50-120 ml/min). The Wright formula appeared to perform no better than the other equations in patients with some degree of renal impairment (GFR<50ml/min).

The use of equations in elderly patients has been explored in other studies,\textsuperscript{28,32-33} one of which studied only patients aged over 100 years, but a reliable equation was unable to be found in these populations.

The International Society of Geriatric Oncology has produced clinical practice recommendations on the assessment of renal function in the elderly.\textsuperscript{31} Summary points of these recommendations include:

1. Before drug therapy in elderly patients with cancer, assessment and optimisation of hydration status and evaluation of renal function to establish any need for dose adjustment is required.
2. These recommendations, for the evaluation of renal function, apply for patients with any type of cancer (decreased renal function occurs in >50% of patients with solid tumors).
3. Serum creatinine concentration alone is insufficient as a means of evaluating renal function.
4. More accurate tools, including CrCl methods such as Cockcroft and Gault, are available and are generally good indices of the renal function status of the patient. In elderly patients however, the Cockcroft and Gault and other similar formulae are not as accurate as in the younger population.
5. More recently developed tools, such as the MDRD, may be the estimation of choice in elderly patients with chronic kidney disease, whereas the Cockcroft and Gault estimate can be used in subjects younger than 65 years.
6. For drug dosing calculations the Cockcroft and Gault formula may be more practical. However, in extremes of obesity and cachexia and at very high and low creatinine values, no single tool is really accurate. The best estimate of GFR is provided by direct methods such as "Cr-EDTA.
7. Coadministration of known nephrotoxic drugs such as non-steroidal anti-inflammatory agents or Cox-2 inhibitors should be avoided or minimised.

**Dose modification of chemotherapy in the elderly - focus on renal function**

Appropriate dosing of chemotherapy in elderly patients is often difficult. Chemotherapy dosing is an individualised process which requires assessment of the patients’ functional status and comorbidities. The most important rule to remember is that treatment should not be withheld or attenuated on the basis of advanced chronological age alone. Complete assessment includes estimation of creatinine clearance as outlined above.

If renal impairment is demonstrated, dose reduction of some drugs may be indicated. Truly evidence-based guidelines on such dose reduction are lacking. The National Cancer Institute Organ Dysfunction Working Group conducts rigorous studies of chemotherapeutics in patients with renal and hepatic dysfunction,\textsuperscript{34} however not all drugs have been studied to date. To further complicate decision-making, dose reduction recommendations are varied depending upon the source of the information. Product information leaflets produced by pharmaceutical companies are often inadequate in dictating the need for dose reduction in patients with renal impairment. A study of four sources of drug information regarding adjustment of dose for renal function revealed variable definitions and a significant proportion of the drugs studied had contradictory information between the different references.\textsuperscript{35}

Work performed by a taskforce of the International Society of Geriatric Oncology has attempted to clarify this situation specifically for the elderly patient population. This group has produced a summary of the recommendations for dose adjustment of most chemotherapy drugs in patients with renal impairment.\textsuperscript{36}

The introduction of the eGFR into routine practice in Australian pathology laboratories has raised awareness of the need to consider CrCl as a measure of renal function rather than spot serum creatinine concentration. This is of utmost importance in the elderly. The current formulae used to estimate CrCl all have failings and their imprecision is exaggerated in patients with low or high GFRs. Although considerable
efforts have been made to help clinicians treating elderly patients, standardized evidence-based guidelines regarding dose reduction in renal impairment are lacking.

References