Renal insufficiency in elderly cancer patients: International Society of Geriatric Oncology clinical practice recommendations

V. Launay-Vacher¹, E. Chatelut², S. M. Lichtman³, H. Wildiers⁴, C. Steer⁵ & M. Aapro⁶*

¹Hôpital Pitie-Salpêtrière, Paris; ²Université Paul-Sabatier and Institut Claudius-Regaud, Toulouse, France; ³Memorial Sloan-Kettering Cancer Center, New York, NY, USA; ⁴University Hospital Gasthuisberg, Leuven, Belgium; ⁵Murray Valley Private Hospital, Wodonga, Australia; ⁶Clinique de Genolier, Geneva, Switzerland

Received 11 October 2006; revised 21 November 2006; accepted 27 November 2006

Background: Elderly cancer patients commonly have renal function decline. This warrants particular caution during the administration of renally excreted cancer drugs or those with established nephrotoxicity.

Design: An International Society for Geriatric Oncology task force was formed to discuss treatment recommendations for this group of patients.

Results: Before drug therapy, the assessment and optimization of hydration status and evaluation of renal function is required. Serum creatinine alone is insufficient as a means of evaluating renal function, and creatinine clearance should at least be calculated in every patient by the abbreviated modification of diet in renal disease or Cockcroft-Gault equations. In the extremes of obesity and cachexia and at very high and low creatinine values, no single tool is really accurate. In these patients, the best estimate of glomerular filtration rate is provided by direct methods such as ⁵¹Cr-EDTA or inulin measurement. Within each drug class, preference may be given to agents less likely to be influenced by renal clearance, which are minimally nephrotoxic, or for which appropriate methods of prevention for renal toxicity exist. Coadministration of known nephrotoxic drugs should be avoided or minimized.

Conclusions: Future trials should be designed to present data in a way that allows evaluation of the contribution of renal function to toxicity and efficacy.

Key words: cancer, clinical practice recommendations, creatinine clearance, elderly, renal insufficiency, SCr

Introduction

Increased life expectancy has led to a significant expansion in the elderly population. By the year 2020, it is estimated that between one-fifth and one-quarter of the population in the Western world will be aged 65 years or more [1]. According to the National Cancer Institute, >60% of all incident cancers and 70% of all cancer-related deaths occur in patients >65 years of age [2] and so there are a significant and rapidly increasing number of older patients who need appropriate cancer care. Physiological changes associated with aging, such as declining renal function and decreasing reserve in multiple organ systems, predispose the elderly to cancer drug toxic effects.

An International Society for Geriatric Oncology (SIOG) task force was formed to discuss optimal clinical practices for treating elderly patients with renal insufficiency. This manuscript outlines the recommendations of this task force, paying particular attention to how renal function should be best monitored.

Renal insufficiency and age

The incidence of chronic renal insufficiency is certainly common among the general population [3] and the prevalence of end-stage renal disease is increasing at a rapid rate with a higher incidence in elderly women compared with men [4]. Patients with malignancies have increasingly been identified with chronic renal failure since the 1970s [5], however the frequency of renal insufficiency in cancer patients is unclear. One study indicates that the frequency is high with one-third of cancer patients presenting with renal insufficiency [6]. The preliminary results of a very recent study, however, showed that the prevalence of renal insufficiency could actually be as high as 60% [7].

Definitions for ‘elderly’ or ‘older’ are somewhat arbitrary, often being divided into groups above and below the age of 65. Some researchers suggest that three categories should be used to define the elderly: the young elderly (65–74); the intermediate elderly (75–84) and the older elderly (85+) [8].

While increasing age is associated with an increased deterioration in physiological status and an increasing risk of contracting diseases, especially cancer, it is also true that age alone is not necessarily a predictor of physiological ‘fitness’.

*Correspondence to: Dr M. S. Aapro, Doyen IMO Clinique de Genolier, 1 route du Muids, 1272 Genolier, Switzerland. Tel: +41-223669106; Fax: +41-223669131; E-mail: maapro@genolier.net

© 2007 European Society for Medical Oncology
Aging is an individualized heterogeneous process and so chronological age does not always predict physiological decline [9, 10]. This means that assessment of function needs to be done on an individual basis in order to ensure therapy appropriateness.

Renal function decline is common in the elderly. As people age, the renal mass shrinks and the age-related reduction in renal blood flow is accompanied by a gradual loss of functioning nephrons. The loss of renal cortical mass reflects a decline in renal function, decreased glomerular filtration and tubular function. Renal function is thus reduced by ~1% per year beyond age 30–40, so that by age 70, renal function may have declined by 40% [11].

The pharmacokinetics and pharmacodynamics of renally excreted drugs are altered in patients with impaired renal function. For many drugs eliminated via the kidneys, use in patients with declining renal function results in reduced elimination, which may necessitate drug dosage adjustment. Anticancer drugs have a narrow therapeutic index, which presents a treatment dilemma for patients with impaired renal function. Dosage of cancer drugs is usually based upon the maximum tolerated dose to achieve best efficacy. Chemotherapy-induced toxic effects are common, but are manageable. In patients with reduced organ function they can, however, result in major organ toxicity. If renal function is impaired and renal clearance reduced, a standard chemotherapy dose will clear more slowly from the body and result in a significantly increased area under the plasma concentration curve (AUC). This may lead to unacceptable toxicity. These issues are particularly acute for agents cleared by the kidney and for those with established nephrotoxicity. Thus, in the elderly, before initiating potentially toxic drug therapy, hydration status should be assessed and optimized and renal function evaluated. The SIOG renal task force have also proposed dose adjustment guidelines for commonly used cancer drugs, which are discussed elsewhere [12].

renal function defined

For chronic kidney disease (CKD), renal function is usually defined by the glomerular filtration rate (GFR), which is the volume of blood/plasma filtered by the glomerulus per minute (and which equates to renal clearance).

In assessing renal function it is standard practice by nephrologists to report GFR normalized to 1.73 m² body surface area (BSA). Thus GFR is reported in the units m/min/1.73 m². The DuBois formula is most commonly used to determine BSA [13].

\[ \text{BSA} = \frac{W^{0.425} \times H^{0.725} \times 0.007184}{0}\]

where BSA is body surface area (m²), W is weight (kg) and H is height (cm).

Adjusting for BSA is necessary when comparing a patient’s GFR with normal values or when determining the stage of CKD [14].

Definitions of normal and abnormal values for renal function vary according to the guidelines followed. Recently, the classification of CKD by staging of renal function has been standardized [15]. A working group of the National Kidney Foundation has published clinical practice guidelines to aid physicians in diagnosing and managing CKD [15] and this system has been adopted in many studies. This classification is now internationally recommended [16]. Stages of CKD were defined from stage 1 to stage 5 (Table 1). In one study, this definition placed 8.3 million USA individuals in the reduced GFR category [17]. The National Kidney Foundation guidelines working group point out that defining renal function using a staging system such as this allows a common language for communication between healthcare providers, ensures more reliable determinations of health risk and treatment efficacy and facilitates the application of clinical practice guidelines, performance measures and quality improvement programs [15].

measurement of renal function

serum creatinine

Estimates of renal function have typically been on the basis of serum creatinine (Scr) levels. Creatinine is an endogenous compound produced mainly from muscle catabolism and released into the blood. The amount produced is relatively stable in a given person. The creatinine concentration in the serum measured in mmol/l or mg/dl (for creatinine, mmol/l = mg/dl × 88.4) is therefore determined by the rate it is being removed, and has been used as a rough measure of kidney function.

Scr concentrations are easy to measure and commonly used in clinical practice but more recent studies have shown that they do not give an accurate indication of renal function [4, 6]. In patients with normal renal function, Scr ranges from 0.8 to 1.3 mg/dl (70–115 μmol/l) in men, and from 0.6 to 1.0 mg/dl (55–90 μmol/l) in women. What makes Scr a difficult index to interpret is that when its value significantly increases, GFR has already decreased by at least 40% (Figure 1).

The rate of Scr production is affected by body mass, muscle mass, diet, drugs, age and sex. Scr should therefore be interpreted with caution in clinical practice. It should not be used as a ‘standalone’ marker of renal function but should only be used in conjunction with other parameters. It is claimed that Scr commonly underestimates renal insufficiency in the elderly [4]. For example, one study showed that, among cancer patients with normal Scr measurements, one patient out of five had asymptomatic renal insufficiency, as assessed by a standard

---

### Table 1. Definitions of degrees of Glomerular Filtration Rate (GFR) decrease

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>GFR (ml/min/1.73 m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kidney damage with normal or increased GFR</td>
<td>≥90</td>
</tr>
<tr>
<td>2</td>
<td>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>

GFR, glomerular filtration rate.
creatinine clearance (CrCl) method [6]. The Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines [18] propose that Scr alone should not be used to assess kidney function. In a study correlating Scr measurement with inulin clearance, 40% of individuals with decreased GFR had an SCr level within the normal range for the laboratory [19].

As muscle mass decreases with age, SCr levels also decrease but this is not always matched by decreased renal function. For example, an SCr level of 1.2 mg/dl may be associated with a CrCl of 110 ml/min (~1.2 mg/dl) in a 30-year-old 90 kg male athlete but only 40 ml/min in a 75-year-old woman weighing 65 kg. In addition, the variation in mean muscle mass that exists between people of different ethnic origin adds further bias to the correlation of SCr measurements with renal function. For an identical weight, the muscle mass of black individuals represents 15% of the total versus 28.7% for white subjects [20], which explains why SCr levels are higher in black than in white people [21].

A further complication in terms of measurement accuracy is the substantial variation that exists between laboratory analytical methods. This is further explained below.

measurement of GFR

A more reliable index of renal function is to measure the renal clearance of a specific marker of glomerular filtration. These markers can be endogenous (e.g. inulin) or exogenous (e.g. radioactive markers including $^{51}$Cr-EDTA, $^{99m}$Tc-DTPA or radiocontrast agents including $^{125}$I-iodomalate). As such markers are excreted only by the glomerulus, they can be measured at intervals to assess clearance rate (indicator decay method). Such methods are widely regarded as the gold standard for measuring GFR. They do, however, require either i.v. infusion and timed urine collections over a period of several hours or several blood samples after i.v. bolus injection. Such methods can be complex, invasive, time consuming, costly and cumbersome. Trained staff are required and the availability of isotopes is a potential problem. In the United States, the radioisotope $^{51}$Cr-EDTA has not been approved by the Food and Drug Administration for use in this test. In other countries, a radioisotope facility may not be easily accessible.

creatinine clearance

CrCl can be either measured using a 24-h urine collection or estimated using formulae on the basis of a single SCr level.

Measurement of creatinine excretion over a 24-h period is a commonly used method, but requires a lengthy and often incomplete collection by the patient at home. This test is thus prone to inaccuracy due to errors in urine collection [18]. In addition, it may provide an overestimate of GFR because creatinine is secreted as well as filtered.

formulae to estimate CrCl

the Cockcroft-Gault method

None of the methods described above are easily employed in daily clinical practice and a simple and rapid bedside method for estimating renal clearance is needed. Several prediction equations for CrCl on the basis of SCr values used in combination with other factors such as age, sex, race and weight have been produced. The most commonly used formula, originating in the 1970s, is the Cockcroft-Gault (C-G) [22]. This equation was derived from a dataset of 249 men, all of whom were inpatients in a veterans’ hospital. The patients were aged from 18 to 92 (mean age 57 years) and 59 (24%) were >70 years of age. The formula was derived using 24-h CrCl values as the standard. Although no females were used in the dataset, the C-G method assumes a reduction in GFR of 15% for this population.

estimated CrCl (ml/min) = \( \left( \frac{140 - \text{age} \times \text{weight}}{72 \times \text{SCr}} \right) \times (0.85 \text{ if female}) \),

where SCr is in mg/dl (SCr µmol/l/88.4 = SCr mg/dl).

Compared with the SCr method, calculating CrCl using such a formula provides a superior estimate of renal function. A recent study of 316 cancer patients showed that the frequency of renal insufficiency measured using SCr was 9.2%. However, when renal insufficiency was estimated by calculating CrCl using the C-G method, 33% of the patients had an estimated GFR of <80 ml/min, which is close to the normal range of 90 ml/min/1.73 m² defined by the internationally recommended National Kidney foundation [6]. In a retrospective medical record review study of 55 patients with severe renal failure assessed by C-G, 30 (54.5%) had SCr values in the normal range [4].

Although recommended as one of the methods of choice when compared with the less accurate SCr assessment [18], the C-G formula was not derived in an elderly cancer-specific population and has been reported to result in a statistically significant underestimation of GFR for decreasing renal function [23]. The formula is not considered to be reliable for obese or edematous patients [24]. The accuracy of the C-G formula has been assessed in a variety of clinical settings and comparisons with direct measures of GFR have almost uniformly concluded that the C-G approximation underestimates GFR for normal and moderately reduced levels of renal function [23, 25–28]. For patients with significantly impaired renal function, the C-G formula overestimates renal function. This is due to the relatively high proportion of creatinine tubular excretion that occurs at low levels of renal function [29]. In the elderly, the C-G formula was shown to produce a consistently low estimate of GFR, a discrepancy most
pronounced in the oldest patients [29]. Others have, however, used it as a standard measure to screen for renal failure in elderly patients and are confident of its validity as a predictive tool in this population [4].

It is of major importance that renal function be assessed at least by calculation of CrCl in every patient, even when SCr is within the normal range.

**the Jelliffe, Wright and Martin formulas**

The Jelliffe [30], Wright [26] and Martin [27] formulas have also been developed to provide improved estimates of renal function.

**Jelliffe formula:**

\[
\text{estimated } \text{CrCl (ml/min/1.73 m}^2\text{)} = \left[98 - 0.8 \times (\text{age} - 20) - \left(1 - (\text{sex} \times 0.1)\right)\right]/\text{SCr},
\]

where SCr is SCr in mg/dl and sex = 0 if male and 1 if female. This formula needs to be uncorrected for BSA (BSA, m²) to yield a result in ml/min by multiplying by BSA/1.73.

The Jelliffe formula was derived in a group of male and female patients without cancer who had undergone renal transplantation and assumes a 10% reduction in CrCl for female patients [28]. As with the C-G formula, the Jelliffe formula was found to result in clinically imprecise estimates of renal function. When compared with the gold standard Tc99m DTPA method, CrCl was underestimated in patients with normal to moderately impaired renal function and overestimated in patients with significantly impaired renal function [23].

The population pharmacokinetic approach was used in the development of both the Wright and the Martin formulas [26, 27]. The resultant estimates of GFR were derived using ⁵¹Cr-EDTA clearance and covariables similar to those in the C-G formula, and the data were derived from patients with cancer.

**Wright formula:**

\[
\text{estimated } \text{CrCl (ml/min)} = \left[650 - (38.8 \times \text{age})\right]/\text{SCr} \times \left[1 - (0.168 \times \text{sex})\right] \times \text{BSA}/\text{SCr},
\]

where SCr is SCr in μmol/l and BSA is body surface area (m²), sex = 0 if male and 1 if female. This version of the Wright formula requires the use of the Jaffé method of SCr measurement.

**Martin formula:**

\[
\text{estimated } \text{CrCl (ml/min)} = \left(163 \times \text{ABW} \times (1 - 0.00496 \times \text{age})\right)/\text{SCr} \times (1 - 0.252 \times \text{sex})/\text{SCr},
\]

where SCr is SCr in μmol/l, ABW is actual body weight in kg, sex = 0 if male and 1 if female.

A retrospective analysis of a large cohort of elderly cancer patients demonstrated the Wright formula to be the most precise and least biased formula over a range of GFR levels [28] when compared with the C-G and Jelliffe formulas. This is in agreement with other groups [23, 26] although neither of these latter studies specifically investigated the elderly. Including a measure of creatinine kinase significantly improves the estimation of GFR with the Wright formula [26].

Studies comparing different formulas using ‘gold standard’ isotope clearance methods have shown considerable variation in outcomes [23, 28] and the bias and precision of these methods when all ranges of GFR are considered should be taken into account. The improved estimate of the GFR using the Wright formula is primarily seen in patients with ‘normal’ renal function (i.e. GFR ≥50 ml/min and <100 ml/min). The formula does have a significant positive bias for low GFR (i.e. overestimates) and a significant negative bias for high GFR (i.e. underestimates) and further comment on recent findings indicates that it cannot be recommended to provide a reliable estimate across the full range of renal function [31]. The Martin formula also results in similar excess bias for high and low levels of GFR and, in addition, has a significant gender bias [27].

Different methods of SCr measurement also affect the predictive accuracy of these formulas. The Jaffé method [32] is a simple, rapid kinetic method that has been in use since the 1970s. It has been replaced in many laboratories by the enzymic PAP (peroxidase antiperoxidase) method [33]. The Jaffé method is known to cross-react with noncreatinine chromogens in serum and so overestimates the SCr level by 5%–15%.

However, renal clearance measured by creatinine is an overestimate of the real GFR, as creatinine is secreted as well as filtered. These two effects neutralize each other and therefore the sum of both may be quite close to the real GFR. The new enzymic method is not influenced by chromogens and is therefore more specific and ensures better interlaboratory consistency than the Jaffé method. This more accurate SCr measurement, however, yields results closer to the actual creatinine level which is higher than the true GFR and might lead to dose overestimation.

A multi-institutional study aimed at improving the carboplatin dosing formula, confirmed the necessity of amending the dosing formula when using the PAP method for the Calvert formula or the C-G equation [22, 34] (Table 2). The formulae were amended for this method by adding 0.2 mg/dl to serum PAP creatinine. Prospective validation of the amended formula showed it to be unbiased and acceptably precise [35]. A prospective study investigated carboplatin dosing according to the Chatelut formula using a SCr value calculation on the basis of the Jaffé assay method. The study recommended an adjustment factor for the SCr value (11.6% decrease) to avoid the underdosing that might result from an overestimation of serum levels [36].

**The Calvert formula:**

\[
\text{CL (ml/min)} = \text{GFR} + 25 \text{ ml/min},
\]

where GFR is the glomerular filtration rate determined by the isotopic ⁵¹Cr-EDTA method.

**The Chatelut formula:**

\[
\text{CL} = 0.134 \times \text{BW} + 218 \times \text{BW} \times (1 - 0.00457 \times \text{age}) \times (1 - 0.314 \times \text{sex})/\text{SCr},
\]

with body weight (BW) in kg, age in years, sex = 0 if male and 1 if female and SCr in μmol/l. For obese patients, mean value between actual and ideal body weight should be used [37].

Despite the superiority of the CrCl estimates over SCr measurements for assessing GFR, various studies have shown that these formulas tend to be less accurate in the elderly and...
in patients with severe renal failure or decreased muscle mass [36, 38–40].

Although CrCl is the preferred method of calculation in clinical practice, it gives only a crude measure of renal function. As renal function declines, tubular secretion and extrarenal elimination of creatinine will increase, thus exaggerating the discrepancy between the clearance of creatinine and whatever is excreted. As renal function declines, tubular secretion and extrarenal elimination of creatinine will increase, thus exaggerating the discrepancy between the clearance of creatinine and whatever is excreted.

**The modification of diet in renal disease formulas**

The so-called modification of diet in renal disease (MDRD) formulas for GFR estimation were derived by computer modeling from the 1628 patients of the MDRD study population [19]. Although mathematically complex, the formulas use readily available patient and laboratory data (sex, age, race, serum albumin and creatinine, urea nitrogen and urinary urea nitrogen) and automatically estimate BSA-indexed GFR rather than estimated CrCl unadjusted for BSA as with the C-G. Several variations on the original formula have been developed. The most precise of these (MDRD6, MDRD7) are on the basis of six different variables and the superiority of these formulas for GFR estimation were derived by computer modeling from the 1628 patients of the MDRD study population [19]. Although mathematically complex, the formulas use readily available patient and laboratory data (sex, age, race, serum albumin and creatinine, urea nitrogen and urinary urea nitrogen) and automatically estimate BSA-indexed GFR rather than estimated CrCl unadjusted for BSA as with the C-G. Several variations on the original formula have been developed. The most precise of these (MDRD6, MDRD7) are on the basis of six different variables and the superiority of these formulas compared with SCr measurements alone provide a significant overestimation of renal clearance, particularly in the elderly [24]. The influence of age and body mass index (BMI) on the performance of the C-G and MDRD formulas was assessed. Both formulas underestimated GFR overall, but in the elderly population (265 years) the C-G formula underestimation was enhanced whereas the MDRD formula blunted the underestimation. The results indicated that the MDRD formula may be the estimation of choice in elderly patients whereas the C-G estimate is preferable in subjects younger than 65 years. In terms of BMI, no reliable estimation could be obtained by using either formula when obesity was present.

In renal transplant patients, all tested MDRD formulas gave a better prediction of true GFR than the commonly used C-G equation and it was suggested that the inclusion of urea nitrogen values in the MDRD equation might improve its predictive ability [38].

<table>
<thead>
<tr>
<th>Method</th>
<th>Formula for renal clearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cockcroft-Gault</td>
<td>Estimated CrCl (ml/min) = [{(140 – age) × weight}/[72 × SCr (mg/dl)²] × 0.85 if female]</td>
</tr>
<tr>
<td>Jelliffe</td>
<td>Estimated CrCl (ml/min/1.73 m²) = [98 – (0.8 × (age–20))] – [1 – (sex × 0.1)]/SCr (mg/dl); sex = 0 if male and 1 if female to give result in ml/min × BSA/1.73</td>
</tr>
<tr>
<td>Wright</td>
<td>Estimated CrCl (ml/min) = [6550 – (38.8 × age)] × [1 – (0.16 × sex)] × BSA (m²)/SCr (µmol/l); sex = 0 if male and 1 if female</td>
</tr>
<tr>
<td>Martin</td>
<td>Estimated CrCl (ml/min) = [163 × ABW (kg) × (1 – 0.00496 × age)] × [1 – 0.252 × sex]/SCr (µmol/l); sex = 0 if male and 1 if female</td>
</tr>
<tr>
<td>MDRD[7]</td>
<td>Estimated CrCl (ml/min/1.73 m²) = (170 × [SCr (mg/dl)]⁻⁰·⁹⁹⁹ × [age (years)]⁻⁰·₁⁷₆ × [0.762 if female] × [1.18 if African American] × [BUN (mg/dl)]⁻⁰·₁⁷⁰ × [albumin (g/dl)]⁻⁰·₁⁰³ × 0.176 × C₀) to give result in ml/min × BSA/1.73</td>
</tr>
<tr>
<td>aMDRD[8]</td>
<td>Estimated CrCl (ml/min/1.73 m²) = (186 × [SCr (mg/dl)]⁻¹·₁₅₄ × [age (years)]⁻⁰·₂⁰₃ × [0.742 if female] × [1.21 if African American]) to give result in ml/min × BSA/1.73</td>
</tr>
</tbody>
</table>

---

8SCr µmol/l = SCr mg/dl × 88.4.

9SCr measured by Jaffe method. If more standardized SCr measurements are used such as peroxidase antiperoxidase, which have recently replaced Jaffe in many institutions, then SCr should be divided by a factor of 0.95 [41, 42].

CrCl, creatinine clearance; SCr, serum creatinine; BSA, body surface area; ABW, actual body weight; BUN, blood urea nitrogen.
Studies recommend that the MDRD equation be used to stratify GFR ranges and to estimate GFR in the general context of oncology therapeutics for GFR-based dosing of antinecancer drugs [19]. It is, however, noted that although the superiority of the MDRD over the C-G formula is established, it is not known whether the formula is similarly accurate in CKD patients with cancer in whom the relationships of SCr, albumin and urea nitrogen may differ from the general population. Preliminary data from the French ‘Insuffisance Renale et Medicaments Anticance´reux’ study confirmed that renal impairment is frequent in cancer patients (n = 1435 in the preliminary analysis) and that SCr measurements are not a reliable index of renal function [44]. Approximately 60% of cancer patients had abnormal renal function (≥90 ml/min/1.73 m²) when the aMDRD method was used but only ~5% had renal insufficiency when the SCr concentrations were used. In the subgroup of 475 patients aged 75 years or more, the prevalence of renal insufficiency by this criterion and using aMDRD was 75% but only 15% of these had raised SCr.

The K/DOQI guidelines recommend the use of the MDRD and C-G equations to predict GFR. However, even though the MDRD equations have been shown to provide a better prediction of GFR than the C-G formula, a large study investigating their applicability to renal transplantation indicated that both formulas failed to reach the level of accuracy required by the K/DOQI standards when compared with the inulin clearance method [43]. Assessment of the predictive performance of these two formulas for estimating renal function showed that both lacked precision and that the C-G formula was less precise than the MDRD one in most cases. The predictive performances of each formula compared with a measured GFR vary according to a variety of conditions, such as sex, BMI and age. Of the subjects, 29.2% and 32.4% were misclassified when the C-G and MDRD formulas were used to categorize subjects according to the K/DOQI classification. Table 2 shows a summary of formulas which can be used to calculate CrCl. While the MDRD formula may be more precise in elderly patients with chronic kidney disease, it has not been shown to be without bias in patients with GFR >60 ml/min/1.73 m². In one study of cancer patients, estimating renal function using cystatin C, there appeared to be no difference between these equations with the exception of patients with severe malnutrition and/or inflammation [45]. However, the MDRD equation is not as practical as the C-G formula as a computer is needed for calculations, and it needs to be corrected for BSA. Therefore, the C-G formula may be best suited for the estimation of GFR for the purposes of drug dosing. No study has been carried out so far to evaluate the benefit of the MDRD compared with other equations to predict carboplatin clearance.

**cystatin C**

An alternative endogenous marker developed to estimate GFR is serum cystatin C, a protein of the cystatin superfamily of cysteine proteinase inhibitors that is expressed in all nucleated cells. It is supposed to meet the criteria for an ideal GFR better than creatinine because it is produced at a constant rate, is not secreted, and is reabsorbed by tubule epithelial cells but subsequently catabolized so that it does not return to the blood flow [46]. It is also independent of age, sex and muscle mass. Studies have also shown cystatin C to be an accurate marker of subtle changes in GFR and diagnostically superior to creatinine with a significantly better correlation with GFR [46]. For patients with reduced renal function receiving cytotoxic drugs, use of cystatin as a marker should improve dose individualization to achieve a target AUC and reduce the likelihood of toxicity. A further potential advantage is the improved precision of the assay compared with that for creatinine, which displays considerable interassay variability, sometimes as high as 25% at low concentrations. A model incorporating both cystatin C and SCr into the formula—along with variables related to muscle mass—was found to be superior to those utilizing either cystatin C or creatinine alone to predict clearance of carboplatin [47]. Similarly, for topotecan, a model on the basis of cystatin C was more predictive for topotecan clearance than models on the basis of creatinine [48].

**Table 3. Summary of recommendations**

| Before drug therapy in elderly patients with cancer, assessment and optimization of hydration status and evaluation of renal function to establish any need for dose adjustment is required. 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 e.g. breast, lung, colorectal, etc.). Patients with tumors affecting the genitourinary tract and/or treated with cisplatin are at a higher risk of renal deterioration (as documented for prostate or ovarian cancers). SCr alone is insufficient as a means of evaluating renal function. More accurate tools, including CrCl methods such as C-G are available and are generally good indices of renal function status of the patient. In elderly patients, however, the C-G and other similar formulas are not as accurate as in the younger population. More recently developed tools, such as the aMDRD, may be the estimation of choice in elderly patients with chronic kidney disease whereas the C-G estimate can be used in subjects younger than 65 years. For drug dosing calculations the C-G 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 51Cr-EDTA or inulin measurement. Within each drug class, preference may be given to agents less likely to be influenced by renal clearance. Within each drug class, preference may be given to agents less likely to be toxic to the kidneys or for which appropriate methods of prevention for renal toxicity exist. Coadministration of known nephrotoxic drugs such as NSAIDS or Cox-2 inhibitors should be avoided or minimized. Future trials should be designed to present data in a way that allows evaluation of the contribution of renal function to toxicity and efficacy. |
conclusions

Renal insufficiency is common in the elderly cancer patient and regular renal monitoring is warranted in this group. This is particularly important in patients receiving renally cleared or nephrotoxic drugs, or in patients with genitourinary tumors (e.g. prostate or bladder cancer) or multiple myeloma. In multiple myeloma, for example, renal involvement due to hematological disease is extremely common. These patients often have preexisting renal problems and are at greater risk of renal impairment caused by drug toxic effects. Renal function should be assessed at least by calculation of CrCl in every patient, even when Scr is within the normal range.

The SIOG Task Force on Renal Safety in the Elderly [44] advocates the consideration of a number of points. The global conclusion is summarized in Table 3.

Dose adjustment of renally cleared drugs is warranted and whenever possible drugs which are cleared via the kidneys or known nephrotoxic agents should be limited or avoided. Dose adjustment recommendations from this task force are reported elsewhere [12].

acknowledgements

The authors would like to thank Gardiner-Caldwell US for their assistance in drafting the manuscript. An unrestricted educational grant was provided by Roche to support the SIOG task force activities.

references