RENAL FUNCTION IN THE ELDERLY

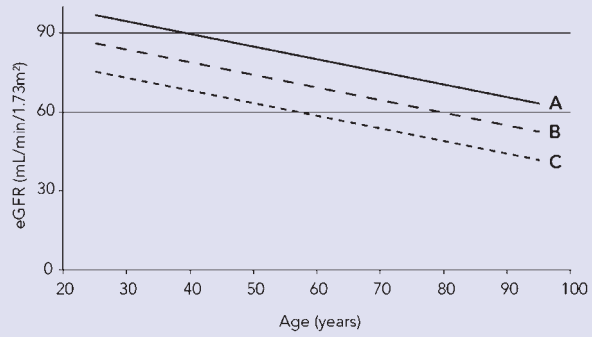
Christopher Steer ■ Border Medical Oncology, Wodonga, Victoria
Email: csteer@bordermedonc.com.au

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.[1, 2] This debate aside, most studies show a decline in GFR with increasing age (Figure 1).

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



*A: 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). ◆

Source: Matthew TH et al. Chronic kidney disease and automatic reporting of estimated glomerular filtration rate: revised recommendations. *MJA* 2007; 187: 459-46319.

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.

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.[3] 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.[4] As the population ages we expect the burden of cancer to be more common, especially in the elderly patient population.

Terminology

Definition of renal failure and stages of chronic kidney disease – American National Kidney Foundation Guidelines.[5]

Stage	Description	GFR (ml/min/1.73m^2)
1	Kidney damage with normal or increased GFR	>90
2	Kidney damage with mild decrease in GFR	60-89
3	Moderate decrease in GFR	30-59
4	Severe decrease in GFR	15-29
5	Kidney failure	<15 (or dialysis)

Chronic kidney disease is defined as either kidney damage or GFR<60ml/min/1.73^2 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.[6]

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.[7] 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:

$$SCr(\mu mol/L) = SCr(mg/100ml) \times 88.4$$

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).[8] 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.[9]

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 1.73m^2. Standardised GFR is reported in ml/min/1.73m^2.

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/1.73^2 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:

$$GFR\ (ml/min) = GFR\ (ml/min/1.73m^2) \times BSA/1.73$$

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}Cr – EDTA ([^{51}Cr]-ethylenediamine tetraacetic acid)

– ^{99m}Tc – DTPA (technetium-^{99m} 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.[10]

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

$$CrCl\ (ml/min) = \frac{(140 - Age) \times wt\ (kg)}{72 \times SCr(mg/100ml)}$$

The formula published by Cockcroft and Gault[11-13] 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

mg/100ml. To convert from μmol/L to mg/100ml, multiply by 0.0113.

2. Jelliffe

$$\text{CrCl (ml/min/1.73m}^2\text{)} = \frac{98\text{-}16((\text{Age}-20)/20)}{\text{SCr(mg/100ml)}}$$

The formula originally described by Roger Jelliffe in 1973 was derived from 128 observations in 15 patients following renal transplantation.[14] Intended as a quick bedside estimate, it asks that the patient's age be rounded to the nearest 10 years. The figure derived from the equation is reduced by 10% in females. A feature of this formula is that the patient's height and weight are not required, however it yields an estimate of "standardised" CrCl in ml/min/1.73m^2 and technically should be "uncorrected" to give a result in ml/min.

3. Wright

$$\text{GFR (ml/min)} = \frac{\{[6550 - (38.8 \times \text{Age})] \times [1 - (0.168 \times \text{Sex})] \times \text{BSA}\}}{\text{SCr (μmol/L)}}$$

SCr – μmol/L (Jaffe method), Sex - male = 0, female = 1, Age – years,

BSA – m^2 Dubois[15] formula $(0.007184 \times \text{weight}^{0.425} \times \text{height}^{0.725})$

This formula was derived in a population of 62 cancer patients.[16] The median age of the population was 58 years (range 23-81). As the "gold standard" used in this study was the ^{51}Cr-EDTA estimation of GFR, this formula is designed to yield an estimate of GFR in ml/min. No conversion is required to calculate doses of renally excreted drugs. The formula was derived using population pharmacokinetic methods. Different formulae were devised depending upon the type of serum creatinine assay used (enzymatic or Jaffe) and if the serum CK was known.

4. eGFR – The revised Modification of Diet in Renal Disease (MDRD) formula (the "175" formula)

$$\text{eGFR (ml/min/1.73m}^2\text{)} = 175 \times (S_{CR} \times 0.0113)^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ [if female]})$$

eGFR = estimated glomerular filtration rate, age = years,

S_{CR} = serum creatinine concentration (μmol/L),

The original MDRD formula was derived from 1704 patients with renal disease.[17] A modified MDRD formula has been recently published.[18] This formula yields a result in ml/min/1.73^2 and requires the patient's age and sex in addition to serum creatinine concentration. To initially derive the formula, glomerular filtration rate measured by the urinary clearance of ^{125}I-iothalamate was used as the "gold standard". The mean age of patients was 50 years. In the updated publication only 2% of participants had a GFR of >90ml/min/1.73m^2.

The eGFR is now reported routinely by pathology laboratories in Australia. As outlined in the position statement from the Australasian Creatinine Consensus Working Group the upper reporting limit has been extended to <90ml/min/1.73m^2.[19] Although the eGFR has been shown to decline with advancing age (Figure 1), age related reference intervals have not been recommended.

The eGFR is intended as a screening tool for patients with renal disease. As it is reported in ml/min/1.73^2 it requires "correction" for BSA if the result is to be used for dosing of renally excreted drugs (see above). 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/1.73m^2.

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.[15, 20-28] 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/1.73^2. Despite this, there has been at least one call for the MDRD to be utilised more widely by cancer physicians.[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.[30] Currently this is the only chemotherapeutic drug that is dosed in this fashion. Other drugs (eg. capecitabine) 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.[31]

The Cockcroft and Gault, Wright and Jelliffe formulae have been compared in a population of 225 elderly patients with cancer.[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,[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.[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 ^{51}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 comborbidities. 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,[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.[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.[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,[31,36-37] standardised evidence-based guidelines regarding dose reduction in renal impairment are lacking.

References

1 Lindeman RD, Tobin J, Shock NW. Longitudinal studies on the rate of decline in renal function with age. J Am Geriatr Soc. 1985;33(4):278-85.

2 Lindeman RD, Tobin JD, Shock NW. Association between blood pressure and the rate of decline in renal function with age. Kidney Int 1984;26(6):861-8.

3 United Nations Department of Economic and Social Affairs Population Division. World Population Ageing: 1950-2050; 2007.

4 AIHW (Australian Institute of Health and Welfare) & AACR (Australasian Association of Cancer Registries). Cancer in Australia 2001. AIHW Cancer Series No. 28 2004.

5 K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 2002;39 (2 Suppl 1):S1-266.

6 Preiss DJ, Godber IM, Lamb EJ, Dalton RN, Gunn IR. The influence of a cooked-meat meal on estimated glomerular filtration rate. Ann Clin Biochem 2007;44(Pt 1):35-42.

7 Mathew TH. Chronic kidney disease and automatic reporting of estimated glomerular filtration rate: a position statement. Med J Aust. 2005;183(3):138-41.

8 Swedko PJ, Clark HD, Paramsothy K, Akbari A. Serum creatinine is an inadequate screening test for renal failure in elderly patients. Arch Intern Med. 2003;163(3):356-60.

9 Tidman M, Sjostrom P, Jones I. A Comparison of GFR Estimating Formulae Based Upon s-Cystatin C And s-Creatinine And a Combination of The Two. Nephrol Dial Transplant 2007.

10 Davila E, Gardner LB. Clinical value of the creatinine clearance before the administration of chemotherapy with cisplatin. Cancer. 1987;60(2):161-4.

11 Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16(1):31-41.

12 Siersbaek-Nielsen K, Hansen JM, Kampmann J, Kristensen M. Rapid evaluation of creatinine clearance. Lancet. 1971;1(7709):1133-4.

13 Cockcroft DW. Creatinine Clearance Prediction - A Citation Classic commentary on prediction of creatinine clearance from serum creatinine by Cockcroft, D.W. and Gault, M.H. Current Contents 1992(48):8 (http://garfield.library.upenn.edu/classics1992/AJX46100001.pdf.)

14 Jelliffe RW. Letter: Creatinine clearance: bedside estimate. Ann Intern Med 1973;79(4):604-5.

15 Dubois D, Dubois EF. A formula to estimate the approximate surface area if height and weight be known. Archives of Internal Medicine. 1916;17:863-71.

16 Wright JG, Boddy AV, Highley M, Fenwick J, McGill A, Calvert AH. Estimation of glomerular filtration rate in cancer patients. Br J Cancer. 2001;84(4):452-9.

17 Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999;130(6):461-70.

18 Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, Kusek JW, Van Lente F. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med. 2006;145(4):247-54.

19 Mathew TH, Johnson DW, Jones GR. Chronic kidney disease and automatic reporting of estimated glomerular filtration rate: revised recommendations. Med J Aust. 2007;187(8):459-63.

20 Dooley MJ, Poole SG, Rischin D. Comparison of bedside estimates of renal function and measured glomerular filtration rate (GFR) in 510 adult oncology patients. . J Clin Oncol ASCO Annual Meeting Proceedings Part I, 2007;25 (18S June 20 Supplement):Abstract 19512.

21 Marx GM, Blake GM, Galani E, Steer CB, Harper SE, Adamson KL, Bailey DL, Harper PG. Evaluation of the Cockcroft-Gault, Jelliffe and Wright formulae in estimating renal function in elderly cancer patients. Ann Oncol. 2004;15(2):291-5.

22 Poole SG, Dooley MJ, Rischin D. A comparison of bedside renal function estimates and measured glomerular filtration rate (Tc99mDTPA clearance) in cancer patients. Ann Oncol 2002;13(6):949-55.

23 Dooley MJ, Poole SG, Rischin D, Webster LK. Carboplatin dosing: gender bias and inaccurate estimates of glomerular filtration rate. Eur J Cancer 2002;38(1):44-51.

24 Lin J, Knight EL, Hogan ML, Singh AK. A comparison of prediction equations for estimating glomerular filtration rate in adults without kidney disease. J Am Soc Nephrol 2003;14(10):2573-80.

25 Pedone C, Corsonello A, Incalzi RA. Estimating renal function in older people: a comparison of three formulas. Age Ageing 2006;35(2):121-6.

26 Planet G. Comparison of creatinine clearance estimates with routine measured clearance. Clin Biochem 2007;40(1-2):124-7.

27 van Warmerdam LJ, Rodenhuis S, ten Bokkel Huinink WW, Maes RA, Beijnen JH. Evaluation of formulas using the serum creatinine level to calculate the optimal dosage of carboplatin. Cancer Chemother Pharmacol 1996;37(3):266-70.

28 Wieczorowska-Tobis K, Niemir ZI, Guzik P, Mossakowska M. Kidney function estimated with different formulas in centenarians. Rocz Akad Med Bialymst 2004;49:219-21.

29 Murray PT, Ratain MJ. Estimation of the glomerular filtration rate in cancer patients: a new formula for new drugs. J Clin Oncol 2003;21(14):2633-5.

30 Calvert AH, Newell DR, Gumbrell LA, O'Reilly S, Burnell M, Boxall FE, Siddik ZH, Judson IR, Gore ME, Wiltshaw E. Carboplatin dosage: prospective evaluation of a simple formula based on renal function. Journal of Clinical Oncology 1989;7(11):1748-56.

31 Launay-Vacher V, Chatelut E, Lichtman SM, Wildiers H, Steer C, Aapro M. Renal insufficiency in elderly cancer patients: International Society of Geriatric Oncology clinical practice recommendations. Ann Oncol 2007;18(8):1314-21.

32 Baracskay D, Jarjoura D, Cugino A, Blend D, Rutecki GW, Whittier FC. Geriatric renal function: estimating glomerular filtration in an ambulatory elderly population. Clin Nephrol 1997;47(4):222-8.

33 Wieczorowska-Tobis K, Niemir ZI, Guzik P, Breborowicz A, Oreopoulos DG. Difference in estimated GFR with two different formulas in elderly individuals. Int Urol Nephrol 2006;38(2):381-5.

34 Takimoto CH, Remick SC, Sharma S, Mani S, Ramanathan RK, Doroshow J, Hamilton A, Mulkerin D, Graham M, Lockwood GF, Ivy P, Egorin M, Schuler B, Greenslade D, Goetz A, Knight R, Thomas R, Monahan BP, Dahut W, Grem JL. Dose-escalating and pharmacological study of oxaliplatin in adult cancer patients with impaired renal function: A National Cancer Institute organ dysfunction working group study. Journal of Clinical Oncology 2003;21(14):2664-72.

35 Vidal L, Shavit M, Fraser A, Paul M, Leibovici L. Systematic comparison of four sources of drug information regarding adjustment of dose for renal function. BMJ. 2005;331(7511):263.

36 Lichtman SM, Wildiers H, Launay-Vacher V, Steer C, Chatelut E, Aapro M. International Society of Geriatric Oncology (SIOG) recommendations for the adjustment of dosing in elderly cancer patients with renal insufficiency. Eur J Cancer 2007;43(1):14-34.

37 Lichtman SM, Wildiers H, Chatelut E, Steer C, Budman D, Morrison VA, Tranchand B, Shapira I, Aapro M. International Society of Geriatric Oncology Chemotherapy Taskforce: evaluation of chemotherapy in older patients--an analysis of the medical literature. J Clin Oncol 2007;25(14):1832-43.