Contents

SECTION 1

Fluid and Electrolyte Disorders in Cancer Patients

1 Kidney Function

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Introduction

Kidney function in oncologic patients is an important parameter for several reasons. In some specific cases, like urologic cancers, the tumor itself can cause acute or chronic kidney dysfunction. However, the renal function parameter is more frequently followed in oncologic patients because, on one hand, they are likely to get nephrotoxic drugs, and on the other hand, some oncologic patients have chronic kidney disease (CKD) that would necessitate a dosage adaptation for potentially toxic chemotherapies.[1,2] Indeed, excretory renal function plays a fundamental role both in the pharmacokinetics and pharmacodynamics of several drugs. This is particularly the case for water soluble compounds and/or their active metabolites. Even for non-renally-excreted drugs, severe CKD can modify the pharmacokinetics by several mechanisms.[3–6] For this reason, it is now recommended that both pharmacokinetics and pharmacodynamics of every new drug be studied in the context of CKD.[7] Dosage-adjustment according to excretory renal function is required for many medications. However, there is a debate in the literature regarding the best way to estimate excretory function or glomerular filtration rate (GFR) for the purpose of pharmacotherapy.[8–12]

Serum Creatinine

The word "creatinine" was probably used for the first time by Justus von Liebig in 1847. This German chemist was thus describing the product obtained from heating creatine with mineral salts.[13] Nowadays, serum creatinine is one of the most frequently prescribed analysis in Clinical Chemistry. Serum creatinine is the only renal plasma biomarker used in daily clinical practice to estimate GFR.[14,15] However, a good interpretation of the creatinine result remains sometimes problematic, or at least not so simple. To explain these difficulties, there are both physiologic (serum creatinine is not an "ideal" renal marker) and analytical reasons. First, serum creatinine can be measured by two main methods: methods derived from the classical Jaffe reaction on one part, and enzymatic methods on the other part. The Jaffe method is based on a reaction between picrate and creatinine in alkaline milieu that gives a red-orange product.[16] Some components (so-called pseudochromogens) can however also interact with picrate: acetoacetate, pyruvate, ketonic acids, proteins, glucose, and ascorbic acid. These pseudochromogens take part in 15% to 20% of the Jaffe reaction if the serum creatinine is in the normal range. This limitation of Jaffe methods remains even after different technological innovations. The second method is known as the enzymatic and is based on successive enzymatic steps. Different types of reactions have been described, but they all share a higher specificity to measure serum creatinine, compared to Jaffe assays. Enzymatic methods are thus considered as more accurate and precise than Jaffe methods. These methods are recommended even if they are more expensive and not fully free from some interferences.[17] There are two methods to measure creatinine but for each method, there are also several different assays (according to the manufacturers). Until recently, a great heterogeneity was observed between the assays, because of differences in calibration.[15,18–20] Nowadays, several improvements have been done in a quest to standardization, and it is recommended to measure serum creatinine with a standardized, calibrated, and so-called *isotope dilution mass spectrometry* (*IDMS*)-traceable method. This traceability is of the highest importance in the context of creatinine-based equations.[15,18–20]

Beyond analytical issues, there are also physiologic limitations to serum creatinine. The molecular weight of creatinine is 113 Daltons. Creatinine is the anhydric catabolite of creatine and phosphocreatine. Creatinine is a catabolite final product and has no physiologic role. The vast majority of creatine (98%) will be found in muscles where creatine is phosphorylated in phosphocreatine by creatine kinase. Each day, 1% to 2% of the muscle creatine is converted into creatinine.[14,21] It is thus obvious that serum creatinine concentration is highly dependent on muscle mass. If the global creatine concentration is constant in healthy subjects, this concentration will strongly vary notably in muscular pathologies or, from a larger point of view, in all diseases with anorexia and muscle mass decreasing, as it is frequently observed in oncologic diseases. In these situations, serum creatinine will decrease, or will not increase when GFR is decreasing.[14,22,23] The second important limitation is the tubular secretion of creatinine, which explains that creatinine clearance overestimated measured GFR (mGFR). Moreover, even if creatinine clearance, calculated on a 24-hour urine collection, is a relatively simple way to assess GFR, such a clearance also lacks precision, especially because of large errors in urine collection.[24] Therefore creatinine clearance is not recommended for GFR estimation.[25] A last point needs to be underlined: the relationship between serum creatinine and GFR is not linear but hyperbolic (Fig. 1.1).[21,26] To keep this point in mind is fundamental for a good interpretation of a creatinine result. Actually, this hyperbolic relation implies that a little creatinine change will have great consequences in terms of GFR in low creatinine levels, although the same creatinine variation in higher ranges will be negligible in terms of GFR.[14,15,20]

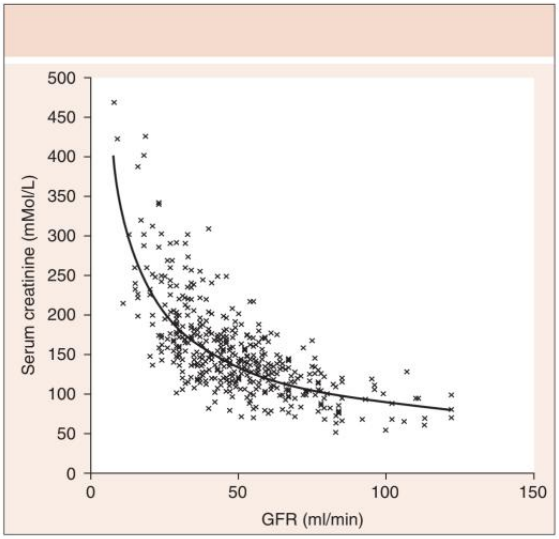

Fig. 1.1 Hyperbolic association between serum creatinine and glomerular filtration rate.

The Creatinine-Based Equations in Oncology

Serum creatinine concentration is dependent on muscular and thus on gender, age, and ethnicity. Moreover, the relationship between serum creatinine and GFR is hyperbolic (see Fig. 1.1). These observations lead authors to propose creatinine-based equations that include simple variables like age, gender, ethnicity and, for some of them, weight.[27–31] Because of the hyperbolic association, a negative exponent is applied to serum creatinine value in these equations, making the association between estimated GFR (eGFR) and mGFR by a reference method, simple and linear. Several equations have been proposed since the 1950s. Before 2000, the Cockcroft and Gault (CG) equation was the most popular and has been used by generations of doctors to estimate GFR.[27] This equation has, however, several limitations, notably a lack of precision caused by the variable weight included in the formula.[32] Today, new equations based on serum creatinine and including only age and gender are recommended and their results can be automatically given by laboratories.[33] These equations are applicable only with IDMS-traceable assays. Among these equations, we can cite the most used, that is, the modification of diet in renal disease (MDRD) equation (most valuable in CKD patients)[28,34] and chronic kidney disease epidemiology (CKD-EPI) equations (also valuable in healthy populations).[29] Recently, some authors have challenged the superiority of these equations both in the general and CKD populations, and proposed new algorithms, known as the *revised Lund-Malmö equation*[31] or the *full age spectrum equations*[30] (Table 1.1). Globally, both in the general or CKD population, one can expect an accuracy around 85% or 90% for creatinine-based equations. This means that results of eGFR equations will be within ±30% of the results of mGFR by a reference method in 85% to 90% of subjects/patients.[35,36] Beyond the experts' discussion to know which equation performs the best, we have to keep in mind that the most important variable in all these equations remains the serum creatinine. Therefore there is no reason to believe that eGFR, by any estimating equations, would be accurate in specific patients or specific populations for who the serum creatinine, in itself, is particularly inadequate.[37] In the context of oncology, it will be particularly relevant in patients with anorexia, loss of weight, and cachexia.[21,38] In these patients, serum creatinine concentration is inaccurate, and can decrease in patients with stable function or remain stable in patients with worsening GFR. Because serum creatinine is inaccurate, eGFR based on serum creatinine will be unable to correctly assess GFR in these patients. In 21 young patients suffering from anorexia nervosa, GFR was measured by a reference method (namely, the ^{51}Cr-Ethylenediaminetetra-acetic acid (EDTA) plasma clearance). The performance of both the CG and MDRD equations was dramatically poor, with an accuracy within 30% of only 63% and 30%, respectively. Both the MDRD and CKD-EPI equations strongly overestimate mGFR in these specific patients.[22] Redal-Baigorri et al. studied the performances of creatinine-based equations in 185 patients with cancer. GFR was measured by ^{51}Cr-EDTA plasma clearance before chemotherapy and serum creatinine was IDMS traceable. Majority of patients were suffering from pulmonary cancer (77%). The performance of MDRD and CKD-EPI was acceptable around 89% for both equations, but most of the patients were healthy from a renal point of view, with only 17% of patients with mGFR below 60 mL/min/1.73m².[39] Lauritsen et al. included patients with disseminated germ cell cancer and treated by bleomycin, etoposide, and cisplatin. The GFR was measured by ^{51}Cr-EDTA single sample plasma clearance in 390 patients, but more than 1600 measurements were obtained with data before and just after chemotherapy, and then after 1, 3 and 5 years. Patients were young with few comorbidities and thus with normal mGFR values. CG, MDRD, and CKD-EPI equations have relatively good performance in estimating GFR before and in the years following chemotherapy (around 85% and 90%). However, values after three cycles of chemotherapy were more disappointing with an accuracy within 30% at 76%, 80%, and 50%, for CG, MDRD, and CKD-EPI, respectively. Actually, mGFR significantly declined during chemotherapy (−9 mL/min/1.73m²) but serum creatinine also decreased (and so eGFR equations increased).[40] Funakoshi et al. also studied the performance of the CKD-EPI equation (both original and Japanese version and de-indexed for body surface area [BSA]) in 50 patients with cancer scheduled for cisplatin therapy (majority had neck and head cancer) before and after treatment. Only subjects with mGFR over 50 mL/min were considered. The accuracy of both CKD-EPI equations was acceptable with an accuracy within 30% of 92% and better than the CG equation (accuracy of 78%) before the therapy. However, a significant decline in accuracy was observed for all equations after the cisplatin cycle: 60%, 68%, and 56% for the original CKD-EPI, the Japanese version, and the CG, respectively. All equations overestimated mGFR, especially in the lower GFR ranges. Moreover, in the

Table 1.1 Creatinine- and Cystatin C-Based Equations to Estimate Glomerular Filtration Rate

Cockcroft and Gault		$((140\text{-age}) \times \text{weight})/(72 \times SCr)$
MDRD		$175 \times SCr^{-1.154} \times age^{-0.203} \times [0.742 \text{ if female}] \times [1.212 \text{ if black}]$
CKD-EPI SCr		
women	SCr ≤ 0.7 mg/dL	$144 \times (Scr/0.7)^{-0.329} \times 0.993^{age} \times [1.159 \text{ if black}]$
	SCr > 0.7 mg/dL	$144 \times (Scr/0.7)^{-1.209} \times 0.993^{age} \times [1.159 \text{ if black}]$
men	SCr ≤ 0.9 mg/dL	$141\times (Scr/0.9)^{-0.411} \times 0.993^{age} \times [1.159 \text{ if black}]$
	SCr > 0.9 mg/dL	$141\times (Scr/0.9)^{-1.209} \times 0.993^{age} \times [1.159 \text{ if black}]$
CKD-EPI SCys	SCys ≤ 0.8 mg/L	$133 \times (Scyst/0{,}8)^{-0.499} \times 0.996^{age} [\times 0.932 \text{ if female}]$
	SCys > 0.8 mg/L	$133 \times (Scys/0{,}8)^{-1.328} \times 0.996^{age} [\times 0.932 \text{ if female}]$
CKD-EPI SCrCys		
women	SCr ≤ 0.7 mg/dL and SCys ≤ 0.8 mg/dL	$130 \times (SCr/0.7)^{-0.248} \times (SCyst/0.8)^{-0.375} \times 0.995^{age} \times [1.08 \text{ if black}]$
	SCr ≤ 0.7 mg/dL and SCys > 0.8 mg/dL	$130 \times (SCr/0.7)^{-0.248} \times (SCyst/0.8)^{-0.711} \times 0.995^{age} \times [1.08 \text{ if black}]$
	SCr > 0.7 mg/dL and SCys ≤ 0.8 mg/dL	$130 \times (SCr/0.7)^{-0.601} \times (SCyst/0.8)^{-0.375} \times 0.995^{age} \times [1.08 \text{ if black}]$
	SCr > 0.7 mg/dL and SCys ≥ 0.8 mg/dL	$130 \times (SCr/0.7)^{-0.601} \times (SCyst/0.8)^{-0.711} \times 0.995^{age} \times [1.08 \text{ if black}]$
Men	SCr ≤ 0.9 mg/dL and SCys ≤ 0.8 mg/dL	$135 \times (SCr/0.9)^{-0.207} \times (SCyst/0.8)^{-0.375} \times 0.995^{age} \times [1.08 \text{ if black}]$
	SCr ≤ 0.9 mg/dL and SCys > 0.8 mg/dL	$135 \times (SCr/0.9)^{-0.207} \times (SCyst/0.8)^{-0.711} \times 0.995^{age} \times [1.08 \text{ if black}]$
	SCr > 0.9 mg/dL and SCys ≤ 0.8 mg/dL	$135 \times (SCr/0.9)^{-0.601} \times (SCyst/0.8)^{-0.375} \times 0.995^{age} \times [1.08 \text{ if black}]$
	SCr > 0.9 mg/dL and SCys > 0.8 mg/dL	$135 \times (SCr/0.7)^{-0.601} \times (SCyst/0.8)^{-0.711} \times 0.995^{age} \times [1.08 \text{ if black}]$
FAS creatinine		$(107.3/SCr/Q_{creat}) \times (0.988(\text{Age-}40))$ if $^{age} > 40$ y
FAS cystatin C		$(107.3/Scyst/Q_{cyst}) \times (0.988(\text{Age-}40))$ if $^{age} > 40$ y
FAS combined		$[107.3/(0.5 \times Scyst/Q_{cyst}+0.5 \times SCr/Q_{creat}] \times (0.988^{(Age-40)})$ if $^{age} > 40$ y
LM	women SCr < 150 μmol/L	$e^{[2.5+0.0121 \times (150\text{-}SCr)]\text{-}0.0158 \times age+0.438 \times Ln(age)}$
	women SCr ≥ 150 μmol/L	$e^{[2.5\text{-}0.926 \times Ln(SCr/150)]\text{-}0.0158 \times age+0.438 \times Ln(age)}$
	men SCr < 180 μmol/L	$e^{[2.56+0.00968 \times (180\text{-}SCr)]\text{-}0.0158 \times age+0.438 \times Ln(age)}$
	men SCr ≥ 180 μmol/L	$e^{[2.56\text{-}0.926 \times Ln(SCr/180)]\text{-}0.0158 \times age+0.438 \times Ln(age)}$
CAPA		$130 \times SCyst^{-1.069} \times age^{-0.117}$ -7

All equations are in mL/min/1.73m² except the Cockcroft-Gault in mL/min.

CAPA, Equation Caucasian, Asian, pediatric, and adult; *CKD-EPI SCr*, Chronic Kidney Disease-Epidemiology Collaboration based on serum creatinine; *CKD-EPI SCys*, equation CKD-EPI based on cystatin C only; *CKD-EPI SCrCyst*, CKD-EPI equation combining both cystatin C and creatinine; *FAS*, equation Full Age Spectrum; *LM*, equation Lund-Malmö; *MDRD*: Modification of Diet in Renal Disease study equation; *SCr*, serum creatinine (in mg/dL); *SCyst*, cystatine C (in mg/L).

postchemotherapy period, one-quarter of patients with CKD-EPI values over 60 mL/min had actually a measured GFR below 50 mL/min.[41] Lindberg et al. also included 94 patients with advanced head and neck cancer treated by radio-chemotherapy including cisplatin. The GFR was measured by ^{51}Cr-EDTA single sample plasma clearance before the first cycle (n=94), after the third cycle of chemotherapy (n=78), and after the planned five cycles (n=35). The nonindexed BSA result was considered for mGFR and eGFR (CG and CKD-EPI). At baseline, five patients were eventually not treated by cisplatin because mGFR was below 50 mL/min. These five patients had eGFR with CKD-EPI above 50 mL/min (and three with CG). At the end of the treatment, three patients had mGFR below 50 mL/min, but this decline in mGFR was detected by both equations in only one patient. The Bland and Altman analyses showed a relatively acceptable systematic bias between mGFR and CG and a systematic overestimation of mGFR by CKD-EPI, but the precision of both equations was actually poor.[42] Hingorani et al. measured GFR by iohexol plasma clearance in 50 patients who benefit from a hematopoietic cell transplant at baseline and after 100 days.[43] The authors compared the performance of mGFR with CG (nonindexed for BSA), MDRD, and CKD-EPI (both indexed for BSA). At baseline, all patients were also treated by trimethoprim, which is known to block the tubular secretion of creatinine, leading to an increase in creatinine concentration independently of any change in mGFR.[44] At baseline, CKD-EPI and MDRD underestimated mGFR and CG overestimated it. The accuracies were low for patients with mean normal GFR values. Indeed, accuracy within 30% at baseline was 79%, 70%, and 57% for CKD-EPI, MDRD, and CG equations, respectively. After 100 days, the accuracy observed was similar for CKD-EPI and MDRD and slightly better for CG.[43] All these data in cancer patients compared mGFR by a reference method with eGFR, but the studies share methodologic limitations, notably the samples being relatively limited. However, it appears from

these analyses that the accuracy of the equations is, at best, suboptimal in cancer patients. This observation is not fully unexpected as these patients are frequently frail and have decreased muscle mass because of their pathology and/or chemotherapy. In the same vein, the inaccuracy of these equations seems especially important during or after the chemotherapy cycles, which is, once again, not fully unexpected.

The Choice of the Equation in Oncology for Drug Dosage Adaptation

Indexing or not GFR by BSA will impact the GFR results particularly in patients or subjects with extreme height and weight values.[45,46] In the context of drug dosage adaptation, it is fully logical to consider nonindexed GFR. This recommendation is supported by the Food and Drug Administration and the European Medicines Agency (EMA). Indeed, the goal of BSA indexation is to make GFR results from subjects with different body size comparable. However, in the context of drug dosage adaptation, the GFR is considered as the capacity of a given subject to excrete drugs or drugs catabolites. As an example, for an elderly fragile woman with a weight of 45 kg, a height of 160 cm, and a BSA of 1.4 m² who is requiring a cisplatin therapy for ovarian cancer, the antimitotic therapy must be dose-adjusted accordingly to her GFR. If her measured (by a reference method) GFR is 25 mL/min, demonstrating a CKD stage 4, BSA indexing will overestimate the GFR to 31 mL/min/1.73 m², classifying the patient as stage 3 CKD. Which result should be used for dose adjustment of nephrotoxic therapy and what stage of CKD should be ascribed to the patient? It seems more correct to take into account the result of the actual patient's GFR, not the GFR result that the patient could have if her BSA was 1.73 m².[45]

If it is thus widely accepted that non-GFR indexed results must be considered for drug dosage adaptation (even if it is not always applied in clinical practice or research), there is still a huge debate in the literature to know which eGFR equation must be considered for drug dosage adaptation. Several publications have illustrated potential discrepancies in eGFR results and thus in dosage prescription if different equations are used.[8,11,47–59] In the context of oncology, Shord et al. retrospectively studied the dose of carboplatin given to the patient with the Calvert formula (Calvert: Total Dose [mg] = [target Area Under the Curve] × [GFR + 25]).[59] They used the CG equation in the Calvert formula for 186 patients. If they had used MDRD, a discrepant dose of carboplatin (defined as a difference of more than 20%) would have occurred in 48% of patients. Bennis et al. considered 1364 cisplatin cycles in 309 patients and observed a requirement for dose adjustment in 9.7% if the CG was used, but 4.8% if the MDRD would have been considered.[57] For drug dosage adjustment, the sharpest debate consists in choosing between the CG equation,[27] frequently promoted by clinical pharmacologists and geriatricians, and the CKD-EPI equation (or MDRD if CKD patients), promoted by nephrologists.[28,29] From a nephrologic point of view, the superiority of the CKD-EPI over CG equation to estimate GFR is easy to demonstrate.[29,32,37] Moreover, this equation truly estimates GFR, whereas the CG equation estimates creatinine clearance, which in itself, is only a poor estimation of true GFR.[37,60] Finally, *sensu stricto*, the CG equation cannot be used with modern, calibrated, and IDMS-traceable serum creatinine values.[19,61–63] Conversely, there are arguments to support the case for applying the CG equation.[4,64–67] Indeed, the CG equation is the equation that has been used to elaborate drug dosage adjustments for the vast majority of drugs.[49,65–69] Furthermore, the CG equation better predicts the risk of adverse events for several drugs, notably cardiovascular therapies. This may reflect the presence of the variable "body weight" in the CG equation, not in the CKD-EPI equation.[11,65,70] Also the CG equation has been reported to give systematically lower eGFR values than those obtained with CKD-EPI, particularly in the elderly.[7,71,72] This underestimation will lead to a more protective behavior in terms of drug dosage in this frail population.[47,73] In a simulation study, we showed that differences between the two equations are potentially influenced by each variable included in these equations: gender, age, weight, height, and serum creatinine. Among these variables, age and weight are the most important and will systematically impact the results of the equations.[7] As an extreme example, in old frail patients, CG will systematically give lower eGFR results than CKD-EPI, but in young obese subjects, CG will systematically give higher results than CKD-EPI. Because drug dosage adjustment is the quintessence of personalized medicine, one should however be careful in our interpretations of differences between eGFR that are based on population studies and focus on the characteristics of the individual.

Other Biomarkers and Measured Glomerular Filtration Rate

In the general healthy or CKD population, new biomarkers have been largely studied. The most promising biomarker was cystatin C.[74–76] Compared with creatinine, cystatin C is presented as being totally, or at least more, independent to muscular mass.[77,78] However, cystatin C is also influenced by other so-called GFR non-determinants, the most important being thyroid function, inflammation, and obesity.[79] Because of few interactions with muscular mass, cystatin C is potentially of interest in the oncologic population. However, data with this biomarker in such a population are few, lack a reference method for measuring GFR, and/or include too few patients.[77,80,81] Chew-Harris et al. compared creatinine CKD-EPI and combined CKD-EPI equations including both creatinine and cystatin C with mGFR by ^{99}Tc-Diethylenetriaminepenta-acetic acid (DTPA) in 80 cancer patients. They showed that the CKD-EPI combined equation (but not the equation based on cystatin C only) was slightly better than the creatinine-based CKD-EPI equation (accuracy within 30% of 83% vs. 78%).[58] Among the studies we have discussed earlier, Hingorani et al. also considered both cystatin C-based and combined equations. At baseline, only the combined equation showed a slightly better accuracy within 30% (at 89%) compared to creatinine-based equations.[43] Because cystatin C is constantly produced by all nucleated cells, there is also the

theoretical possibility that cancer cells produced cystatin C with an increase in cystatin C concentrations without any change in GFR values.[26] However, too few data are available to close the debate.

In oncology, drug dosage adjustment is thus influenced by the choice of the creatinine-based equation, as discussed in the prior paragraph. However, because any eGFR is far from perfect, there is a risk that all equations are inadequate for drug adjustment. A definitive conclusion could only be given by a prospective observational randomized study, where patients would get chemotherapy dosage according to mGFR in one group, and to different eGFR equations in other groups. Efficacy, cancer recurrence, and safety of the chemotherapy could then be compared between the different groups. However, such a study is not available. We have only retrospective data where the dosage of the chemotherapy (calculated with the Calvert formula) obtained with mGFR is compared, by retrospective simulations, with dosage that would have been used if eGFR had been considered instead of mGFR. Several studies performed such an analysis in oncologic patients and all these studies suggest that eGFR (whatever the equation) can lead to significant different dosage than the dosage based on mGFR effectively given to the patient.[49,50,54–56,58] Ainsworth et al. showed data obtained from 660 cancer patients treated by carboplatin. GFR was measured by ^{51}Cr-EDTA. A significant different dose (defined as a difference larger than 20%) was observed in 22% and 32% of cases for CG and MDRD, respectively.[49] In the same type of patients, Craig et al. observed in their 175 subjects that eGFR would have led to a higher dose (> 20%) in 26%, 30%, and 36% of patients with CG, MDRD, and CKD-EPI, respectively.[50] Dooley et al. measured GFR with ^{99}Tc-DTPA in 455 patients treated by carboplatin. They showed a potential discordant dose in 36%, 33%, and 29% of cases for CG, MDRD, and CKD-EPI, respectively, with a high proportion of underdosing with eGFR.[54] Shepherd et al. and Cathomas et al. both studied young patients with seminoma and treated by carboplatin. Both also used the Calvert equation for the dosage adjustment and the dose was determined with GFR measured by ^{51}Cr-EDTA (mixed with ^{99}Tc-DTPA in the Cathomas study).[55,56] Shepherd, in his simulation including 115 patients, showed that, if an error of 20% was considered in the drug dosage, such a difference would have been observed in 33% of patients with (nonindexed) CG (only 1% of underdosing, the rest being overdosing), in 22% with indexed CG (50/50 underdosing and overdosing), 28% with CKD-EPI (6% overdosing and 22% underdosing), and 14% with de-indexed CKD-EPI (11% overdosing and 3% underdosing). If an error of 10% was considered as relevant, the same dose between mGFR and all eGFR equations would have be given in less than 50% of patients.[55] In the Cathomas study, 426 patients were included. A significant overdosing was considered if the difference was over 125% and an underdosing if the difference was less than 90%. Overdosing prevalence would have been 7% and 1% in CG (nonindexed) and CKD-EPI (de-indexed), respectively. Underdosing would have reached 18% and 41%, respectively.[56] Again, all these studies are simulations, but they share the similar key message: using eGFR instead of mGFR for drug dosage adjustment of cis- or carboplatin would lead to significant different doses. Overdosing can potentially lead to more secondary effects, and thus concerns with safety and underdosing would lead to a significant higher risk of disease recurrence, which is relevant, for example, in young patients treated for seminoma. From these studies, it remains, however, difficult to definitively assert that one equation will lead to overdosing and that another will underdose, because studies are different in their methodologies (different equation considered, serum creatinine IDMS traceable or not, results indexed by BSA or not, use of actual weight or ideal weight in the CG, etc.) and in their populations. If the debate still exists between different eGFR equations for drug adaptation until now, the solution could be, at least in part, in simplified protocols that used measured GFR and reference methods. For this option, it seems that iohexol plasma clearance is certainly the best balance between feasibility and physiology.[82] Of interest, the EMA is now recommending that the manufacturer performs studies with mGFR (and not eGFR) for new therapies that require a dose adjustment according to CKD staging.

Conclusions

Patients with cancer are at high risk of acute or chronic renal failure. Therefore the most exact estimation of GFR is required. Because of the frequently observed anthropometrical characteristics of oncologic patients (declining muscular mass), serum creatinine and thus creatinine-based equations are frequently inaccurate, leading to over- or underdosing of drugs. There is still a debate in the literature about the best creatinine-based equation to be used for drug dosage adjustment. Having said that, there is indirect proof that all equations could be misleading, and some authors argue for using mGFR to adjust drug dosage in cancer patients. No randomized prospective study strongly supports the necessity of mGFR in oncology. However, based on the available literature, we and others would recommend considering mGFR for drug dosage adjustment at least in case of chemotherapy with a potentially nephrotoxic drug and with a narrow therapeutic index, the best example being cis- or carboplatin. In other cases, different eGFR equations can be used and the doctor can calculate the absolute and relative difference between the two equations, flagging up discordant cases (difference of > 10 mL/min or > 10%). If results are concordant, the clinician can reasonably apply drug dosage recommendations available in the literature. If discrepancies occur, it would be important to consider the characteristics of the patients and the safety profile of the drug considered. For highly effective concentration-dependent drugs, the risk of underdosage (and thus risk of cancer recurrence) could be as important as the risk of overdosage, especially if the risk of nephrotoxicity is relatively low. In such cases, it could be more efficient to consider the equation that gives the higher GFR results. Conversely, it could be better to recommend adjusting the dosage of a drug to the equation giving the lower result if the prescription concerns potentially nephrotoxic drugs.[7,66]

Key Points

1. Measuring kidney function is important in patients with cancer to allow appropriate drug dosing and monitoring for development of acute and chronic kidney disease.
2. Serum creatinine is the most widely used test to estimate kidney function despite its limitations.
3. A number of formulae (CKD-EPI, MDRD, CG, etc.) are used to estimate glomerular filtration rate (eGFR), all that have limitations in the individuals studied (because of age, muscle mass, etc).
4. Cystatin C plus creatinine has also been used to calculate eGFR; however, the data are limited at this time, making it premature to draw a conclusion.
5. Measuring GFR (^{99}Tc-DTPA, ^{51}Cr-EDTA, iohexol plasma clearance, etc.) is more cumbersome but is likely the best test to use, when dosing chemotherapeutic agents that are potentially nephrotoxic and have a narrow therapeutic window.

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2 Dysnatremias in Cancer

UMUT SELAMET AND ALA ABUDAYYEH

Hyponatremia

HYPONATREMIA AND CANCER RELATIONSHIP

Hyponatremia is the most common electrolyte abnormality observed in cancer patients. In a retrospective cohort study from a comprehensive cancer center, hyponatremia (serum $Na^+ < 137$ mEq/L) was noted in 47% of hospitalized cancer patients [VO2].[1] In general, hyponatremia is categorized as mild (130–134 mEq/L), moderate (120–129 mEq/L), and severe (< 120 mEq/L), according to serum sodium concentrations.[2] Hyponatremia has been linked to poor prognosis in several types of cancers, which include non-small cell lung cancer, pleural mesothelioma, renal cell carcinoma, gastrointestinal cancer, and lymphoma.[3,4] The risk of mortality increases with more severe hyponatremia.[5] Moreover, low serum sodium concentrations have also been associated with poorer performance status in lung cancer patients.[6] In addition, timely and effective corrections of serum sodium concentrations have been associated with improvement in prognosis for several cancers.[7,8]

SYMPTOMS

Symptoms of hyponatremia are caused primarily by osmotic swelling of brain cells and increased intracranial pressure (ICP).[9] Severity of symptoms usually correlates with the degree of hyponatremia. Most patients with mild to moderate hyponatremia are asymptomatic. Severe hyponatremia, on the other hand, may cause nausea, vomiting, confusion, falls, movement disorders, seizures, and coma. Time course of the development of hyponatremia is another significant factor that determines the severity of symptoms. Chronic hyponatremia (onset > 48 hours) can be asymptomatic whereas acute hyponatremia can manifest as encephalopathy, especially in patients with malnutrition, hypokalemia, alcoholism, or advanced liver disease.[10]

PATHOPHYSIOLOGY

Hyponatremia is the result of imbalance between salt and water concentrations with relatively more total body water (TBW) than salt. Normal kidneys can eliminate up to 20 to 30 L of free water daily.[11] Antidiuretic hormone (ADH) also known as *arginine vasopressin* (*AVP*) is the major hormone that regulates free water reabsorption by kidney tubules. ADH is a peptide hormone produced by the hypothalamus and transported to the posterior pituitary via nerve axons. It is released into the circulation from the posterior pituitary and binds to V2 receptors at the basolateral side of the collecting tubules in the kidney. Binding of ADH to V2 receptor activates adenylate cyclase and subsequent formation of cyclic adenosine monophosphate (cAMP). This leads to movement and fusion of specific vesicles that contain aquaporin 2 (AQ2) channels in the cytoplasm to the apical membrane of the collecting tubules. Once AQ2 channels are inserted, the apical membrane becomes permeable to water. Water moves from medullary renal space to the apical membrane and is then released into the circulation through the basolateral membrane (Fig. 2.1). ADH release is stimulated by two mechanisms: osmotic and nonosmotic factors. The osmotic regulation of ADH occurs in the anterior hypothalamus as "osmoreceptor cells or osmostat" sense changes in extracellular fluid (ECF) osmolality. This is a tightly controlled system as an increase or decrease in ECF osmolality by 1% stimulates or suppresses ADH release respectively. Nonosmotic stimulation of ADH release occurs in the absence of changes in serum osmolality. Pain, emotional stress, nausea, and reduction in effective arterial blood volume (EABV) are some of the examples of nonosmotic stimuli, which tend to be very common in patients with cancer and those under treatment with various cancer therapies.

APPROACH TO ETIOLOGY OF HYPONATREMIA

Hyponatremia typically develops when there is disruption in the elimination of free water by kidneys, or when water shifts from the intracellular to extracellular space, both of which result in the dilution of extracellular sodium concentration. Several algorithms are considered acceptable when evaluating a patient with hyponatremia. The most commonly used algorithm incorporates both serum osmolality and urine sodium concentrations. We have adopted this approach for specific causes of hyponatremia in cancer patients (Fig. 2.2).

The first step in a patient with hyponatremia is to check serum osmolality. Serum osmolality is normally tightly maintained between 280 to 290 mOsm/L. Using this range, hyponatremia can be classified as hyper-osmolar, iso-osmolar, and hypo-osmolar hyponatremia.

Hyper-Osmolar Hyponatremia

If serum osmolality increases because of an effective osmole other than sodium, then hyper-osmolar hyponatremia develops as the effective osmole causes water shift from intracellular to extracellular space. The most common example of this kind of hyponatremia is caused by hyperglycemia. For each 100 mg/dL increase in plasma glucose, above 150 mg/dL 1.6 to 2.4 mEq/L decrease is observed in serum sodium concentration.[12] Hyperglycemia over time can also stimulate thirst and ADH secretion by causing low EABV secondary to osmotic diuresis.[13]