

Carboplatin Dosing in Real Life: Beyond Estimating Glomerular Filtration Rate and the Virtue of Simplicity!

Sir,

Several chemotherapeutic agents have a narrow therapeutic index, and accurate dosing becomes essential to avoid toxicity, such as myelosuppression or gastrointestinal toxicity. Weight-based dosing, body surface area (BSA)-based dosing, and area under the curve (AUC)-based dosing are commonly employed to estimate doses of anticancer agents.^[1] Of these, AUC-based dosing (area under the plasma concentration multiplied by time) is the most relevant for drugs which are eliminated by the kidneys. For drugs which have nonrenal elimination or multiple pathways for elimination, AUC-based dosing is not useful. In routine oncologic practice, the carboplatin dosage is usually estimated based on AUC-based dosing since carboplatin clearance closely matches creatinine clearance. Therein lies the importance of measuring or estimating creatinine clearance.

Certainly, measuring the glomerular filtration rate (GFR) using ⁵¹I-labeled ethylenediaminetetraacetic acid would be the most accurate. However, this is not usually available at most centers, and in actual oncologic practice, the GFR is estimated rather than measuring. Several equations have been developed in the past for estimating GFR which include Cockcroft–Gault equation and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, among several others. Recently, in an article by Janowitz *et al.*, we came across a newer, more accurate, albeit cumbersome method to estimate creatinine clearance. The authors used a robust methodology and developed and validated a model to accurately predict the measured GFR.^[2] However, while deciding the dosage of carboplatin (the primary drug for which these equations are utilized), several factors other than estimated GFR (including but not limited to performance status [PS]) merit consideration. The key question is whether we require such a high degree of precision in estimating GFR in real-life settings? The argument to support this is that, if accuracy was the only essential criteria, we might be measuring the GFR in all patients rather than estimating. Yet in routine clinical practice, we avoid doing the former as it is not easily available. The same argument would probably also hold true for the newer model proposed by Janowitz *et al.* It is indeed accurate and precise, yet remains complex and inaccessible for a vast majority. Even though the authors have tried to simplify the calculation by providing an online tool, the bottom line is that it still remains fairly complex even for people working in academic settings. The major burden of cancer is currently in the developing and underdeveloped nations.^[3] Oncologists practicing in resource-constrained settings may

not have ready access to an online tool, and the simple desk calculator is often what they have.^[4] Further, each equation developed in a specific population needs to be validated in other ethnic and geographic areas before attempting its application/generalization.

We performed an *ad hoc* retrospective audit of lung cancer patients undergoing first-line chemotherapy at our center, with the aim of determining discrepancies between actual doses of carboplatin administered in the first cycle versus those calculated using different equations for GFR estimation. The Calvert formula was used to calculate carboplatin dose, with the estimated GFR being obtained from Cockcroft–Gault equation, CKD-EPI equation, and the Janowitz *et al.*'s equation.^[2] Carboplatin dose was also calculated using manufacturer's instructions (BSA in kg/m² × 300 for GFR >60 mL/min; BSA × 250 for GFR = 41–60 mL/min; and BSA × 200 for GFR ≤40 mL/min). Dose derived from GFR estimated using the Janowitz *et al.*'s online tool was considered as the reference standard. Absolute dosage differences and percentage errors (PEs) for the above equations were calculated.

From January 1, 2017 till August 31, 2017, 77 patients received carboplatin-based chemotherapy. Dosage calculated by Cockcroft–Gault-based GFR and manufacturer's recommendation had significant variation as compared to the authors' new equation-based carboplatin dose [Table 1]. The dosage calculation based on CKD-EPI equation was largely similar to the latter. However, the actual administered doses (with reductions being made for PS and vial package strengths) were lower than both Cockcroft–Gault-based doses and manufacturer's recommended doses (both of which are routinely used at our center for dose calculations).^[5,6] A significant proportion ($n = 48$, 62.3%) had >20% absolute PE of carboplatin dose as compared to the reference standard. Carboplatin dose PEs (actually administered, calculated as per Cockcroft–Gault equation, manufacturer's recommendation and CKD-EPI equation) were plotted as a waterfall chart [Figure 1a-d]. All, except six (7.8%) patients, received doses less than or equal to that calculated from the reference. None of the above six received carboplatin dose ≥20% than the predicted reference. Hypothetically, even if the administered carboplatin dose was exactly as calculated from Cockcroft–Gault equation and manufacturer's recommendation, majority (83.1% and 81.8%, respectively) would have still received a lower dose compared to the reference and those receiving ≥20%

Table 1: Comparison of carboplatin dose estimation based on different methods and their percentage errors compared to the reference standard

Method of dose calculation	Median (IQR) dose in mg	Residual dose, median (IQR) mg	Median PE (%) IQR	Median APE (%) IQR	Number of patients with APE >20%, n (%)
Cockcroft-Gault based	434.1 (382.5-513.9)	-50 (-69--14)	-12.5 (-17.3--2.79)	17.9 (7.2-28.6)	18 (23.4)
CKD EPI based	515.5 (434.6-567.4)	11.1 (-8.8-23.7)	2 (-1.7-4.4)	3.5 (2.1-5.0)	2 (2.6)
Manufacturer-recommended doses	447.5 (380-501)	-59.2 (-123.9--13.6)	-13.6 (-28.7--3.3)	13.3 (5.2-18.6)	36 (46.8)
Actual dosage given	400 (350-450)	-106.9 (-160.8--57.5)	-26.8 (-45.3--13.5)	27.1 (14.7-45.3)	48 (62.3)

APE – Absolute percentage error; CKD EPI – Chronic Kidney Disease Epidemiology Collaboration; IQR – Interquartile range; PE – Percentage error

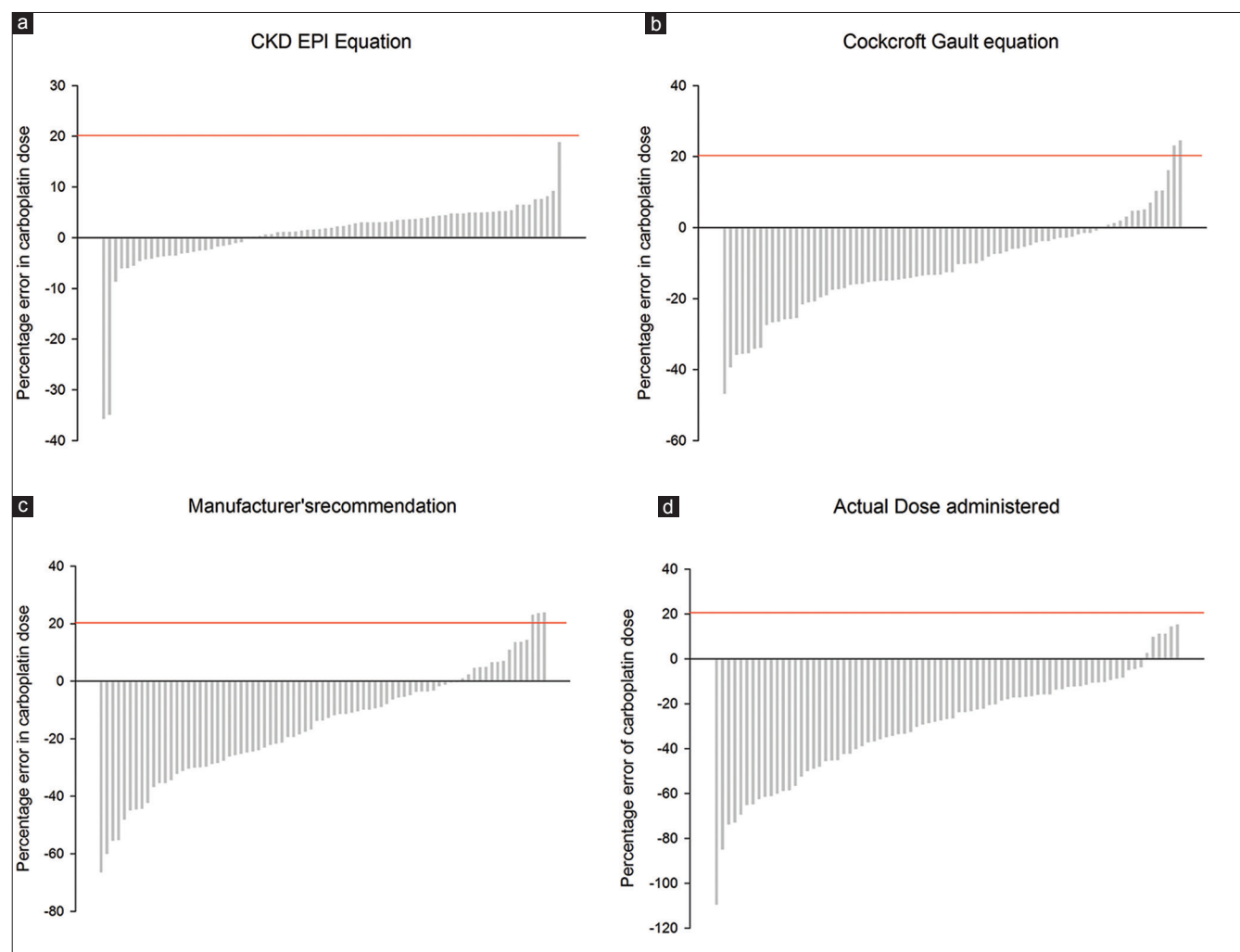


Figure 1: Waterfall plot shows the percentage error in the carboplatin dosage along Y-axis (each bar represents one patient); (a) dose calculated as per the Chronic Kidney Disease Epidemiology Collaboration equation, (b) dose estimated by the Cockcroft–Gault equation, (c) dose estimated as per the carboplatin manufacturer's recommendations, and (d) the dose which the patients actually received at our center. The comparator in all these plots was the dosage calculated as per the reference standard (glomerular filtration rate based on the new equation proposed by Janowitz *et al.*). Red line marks the 20% excess dose from the reference dosage

overdose would have been only two (2.6%) and three (3.9%) patients, respectively [Figure 1b and c].

Thus, the actual dose administered to patients is lower than that predicted in the majority, often due to PS and vial package strength issues. This is irrespective of what equation one uses to estimate GFR. Hence, the probability of administering an unacceptable and potentially

toxic (higher) dose of carboplatin, based on an incorrect GFR estimation, might be much lower in clinical practice than what one would expect. It is good to be accurate, but it is even better to be safe and simple. While we accept the inadequacies in estimating GFR by the currently available equations, the actual administered carboplatin doses that patients generally receive can be safely and

conveniently calculated with these equations without the requirement for having to access a complex equation online each time – something that is of particular relevance in resource-constrained settings. Therefore, we believe that using more accurate newer equations may not be required as multiple factors influence the final administered dose.

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Conflicts of interest

There are no conflicts of interest.

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