Letter To Editor

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

Sir,

Several chemotherapeutic agents have а narrow accurate therapeutic index. and 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 51-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 \times 300 for GFR >60 mL/min; BSA \times 250 for GFR = 41–60 mL/min; and BSA \times 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 carboplatin-based chemotherapy. received 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 $\geq 20\%$ 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 $\geq 20\%$

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

Method of dose	Median (IQR) dose	Residual dose,	Median PE (%)	Median APE	Number of patients		
calculation	in mg	median (IQR) mg	IQR	(%) IQR	with APE >20%, n (%)		
Cockcroft-Gault based	434.1 (382.5-513.9)	-50 (-6914)	-12.5 (-17.32.79)	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 (-123.913.6)	-13.6 (-28.73.3)	13.3 (5.2-18.6)	36 (46.8)		
Actual dosage given	400 (350-450)	-106.9 (-160.857.5)	-26.8 (-45.313.5)	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.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Valliappan Muthu, Kuruswamy Thurai Prasad, Navneet Singh

Department of Pulmonary Medicine, Postgraduate Institute of Medical Education and Research, Chandigarh, India

Address for correspondence:

Dr. Navneet Singh, Department of Pulmonary Medicine, Postgraduate Institute of Medical Education and Research, Sector-12, Chandigarh - 160 012, India. E-mail: navneetchd@hotmail.com

References

- Gao B, Klumpen HJ, Gurney H. Dose calculation of anticancer drugs. Expert Opin Drug Metab Toxicol 2008;4:1307-19.
- Janowitz T, Williams EH, Marshall A, Ainsworth N, Thomas PB, Sammut SJ, *et al.* New model for estimating glomerular filtration rate in patients with cancer. J Clin Oncol 2017;35:2798-805.
- 3. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A, *et al.* Global cancer statistics, 2012. CA Cancer J Clin

2015;65:87-108.

- Singh N, Aggarwal AN, Behera D. Management of advanced lung cancer in resource-constrained settings: A perspective from India. Expert Rev Anticancer Ther 2012;12:1479-95.
- Singh N, Singh PS, Aggarwal AN, Behera D. Comorbidity assessment using charlson comorbidity index and simplified comorbidity score and its association with clinical outcomes during first-line chemotherapy for lung cancer. Clin Lung Cancer 2016;17:205-130.
- Singh PS, Aggarwal AN, Behera D, Kapoor R, Singh N. Simplified graded baseline symptom assessment in patients with lung cancer undergoing first-line chemotherapy: Correlations and prognostic role in a resource-constrained setting. J Glob Oncol 2017;3:54-63.

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

Access this article online				
Quick Response Code:	Website:			
	www.ijmpo.org			
	DOI: 10.4103/ijmpo.ijmpo_8_18			

How to cite this article: Muthu V, Prasad KT, Singh N. Carboplatin dosing in real life: Beyond estimating glomerular filtration rate and the virtue of simplicity! Indian J Med Paediatr Oncol 2019;40:155-7.

© 2019 Indian Journal of Medical and Paediatric Oncology | Published by Wolters Kluwer - Medknow