

Pharmaceutical Science Committee Meeting Conference call

Date: March 17, 2020; 12 noon – 1 pm PST

Purpose: Review of current SWOG Policy #38 focusing on the Creatinine Clearance (CrCl) estimation recommendations to align with the NCCN and GOG carboplatin dosing CrCl estimation guidelines

A recent inquiry was made by the SWOG investigators at the University of Kansas regarding the use of minimum serum creatinine (SCr) level of 0.7 mg/dL instead of 0.8 mg/dL to estimate subject's CrCl when a subject has a measured serum creatinine level lower than 0.8 mg/dL. The rationale to restrict the body weight and SCr in the calculation is to minimize the risk of over-estimation of a subject's CrCl who is obese and has low SCr. This can lead to inappropriate protocol screening and dosing of medication. The inquiry stemmed from the current guidelines of NCCN and GOG have set the minimum SCr at 0.7 mg/dL for the calculation of carboplatin dosing, therefore a consistent policy at SWOG will be optimal.

A total of 9 committee members attended the conference call and they all represented different institutions ranging from Florida to California. A quick survey indicated the majority of the institutions use the minimum SCr of 0.8 mg/dL for the age group ≥ 65 yo, and 0.7 mg/dL for age < 65 yo. Review of recent literatures in nephrology appear to indicate that use of patient's actual SCr provides fairly accurate estimation of their CrCl irrelevant of the SCr levels. The committee recognizes that the slight variations among the practice sites represented in the call are not based on evidence-based guidelines because they are not available. The committee also wish to promote the use of the SWOG online CrCl estimation tool to reinforce consistency in the estimation of CrCl, therefore manual adjustments by the site investigators should be discouraged. Following a comprehensive discussion, the committee unanimously agreed to modify the current SWOG Policy #38 to change the minimum SCr from 0.8 mg/dL to 0.7 mg/dL, and to extend the capping of the estimated CrCl to 125 ml/min to all scenarios and no longer limit that to carboplatin dosing only. The committee feels that the capping of the CrCl will serve to minimize the potential increased risk of overestimation of the CrCl in lowering the minimal SCr to 0.7 mg/dL. Furthermore, this modification will align with the NCCN and GOG guidelines, thereby can minimize risk of protocol deviation/violation by the site investigators without compromising patient safety.

In conclusion, the committee will:

- 1. Revise the current SWOG Policy #38 to change the minimal SCr from 0.8 mg/dL to 0.7 mg/dL in the Cockcroft-Gault equation, and to extend the capping of the estimated CrCl of 125 ml/min to all scenario. The revised policy will be forwarded to Courtney Willis for Board of Governor approval.**
- 2. Following the approval of the policy, the recommendations will be forwarded to the statistical center to incorporate the modification in the SWOG online calculator tool and to encourage all site investigators to consistently used this tool for all SWOG protocol-related interventions.**

Policy Memorandum No. 38
Subject: Dosing Principles
Departments Affected: All

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Original Release Date: October 2001
Revision Date: ~~October 2017~~ ~~March~~ ~~Fall~~ 2020

DOSING PRINCIPLES FOR PATIENTS ON CLINICAL TRIALS

I. TREATMENT DOSING BASED ON BODY SURFACE AREA

1. Background

Body surface area (BSA) is a mathematical function of height and weight to allow for extrapolation of drug dosing from lower mammals to humans. BSA-based dosing eventually found its way to become the requirement for the Food and Drug Administration-approved labeling. Subsequent generations of oncologists also viewed BSA-based dosing as a standard training for the safe and effective administration of cytotoxic chemotherapy.

The use of ideal versus actual body weight in determining BSA, especially in obese patients, remains controversial. Numerous published studies over the last 2 decades continued to support the findings that the use of actual body weight in dosing chemotherapy for the obese patients (defined as BMI ≥ 30), especially in the adjuvant setting do not have poorer prognosis and no increased toxicity was observed (Georgiadis, et al. J Natl Cancer Inst 1995 1;87(5):361-6, Rosner, et al. J Clin Oncol 1996;14(11):3000-8, Meyerharsdt, et al. Journal of Clinical Oncology 2004;22(4):648-57, Barrett, et al. Annals of Oncology 2008;19(5): 898-902). A review article by Hunter et al. (Cancer Treatment Review 2009;35(1):69-78), a pharmacokinetic study by Sparreboom et al. (Journal of Clinical Oncology 2007;25(30):4707-4713), and an editorial by Gurney et al. (Journal of Clinical Oncology 2007;25(30):4703-04) strongly discouraged the use of capped BSA in the dosing of chemotherapy drugs in obese patients. Considering the variation in the dosing of chemotherapy in overweight and obese individuals with cancer, an ASCO guideline published in April 2012 (Griggs et al Journal of Clinical Oncology 2012; 30(13):1553-61) provided the first consensus practice guideline on chemotherapy dosing for obese adult patients with cancer. The panel recommends full weight-based cytotoxic chemotherapy doses be used to treat obese patients with cancer, particularly when the goal of treatment is cure. Based on the data evaluated, the following recommendations are being proposed for BSA-based drug dosing in research protocol patients.

2. Initial Dosing

Actual body weight of a patient should always be used to calculate the body surface area for drug dosing. Body surface area can be determined from weight and height by using a nomogram found in standard references or the Mosteller Formula as indicated below.

$$BSA (m^2) = \sqrt{(Ht \text{ in cm}) \times (Wt \text{ in Kg}) \div 3600}$$

If the actual body weight of the patient is more than two times the ideal body weight, that patient should only be considered for protocol treatment if the treating physician feels comfortable that the protocol treatment as *written* would be a reasonable choice for the patient. Otherwise, drug dosing of patients for off-protocol treatment is at the discretion of the health care provider of the patient.

Formula for calculation of IBW:

Male = 50 kg + (2.3 kg x number of inches above 60 inches)

Female = 45.5 kg + (2.3 kg x number of inches above 60 inches)

For patients whose height is less than 60 inches, the estimation of ideal body weight or lean body weight are inconsistent at extremes of size using the current methods. A study by Janmahasatian S et al (Clinical Pharmacokinetics 2005;44(10):1051-1065) developed a model that incorporated gender, height, and bodyweight to predict fat-free mass (FFM). Using the dual-energy x-ray absorptiometry, a referenced objective measurement, and bioelectrical impedance analysis data, the authors prospectively evaluated this model in a study population between 18-82 years old, height between 54.2 -82.2 inches, bodyweight between 40.7-216.5 kg and BMI values from 17.1-69.9 kg/m². The predictive performances of the model in estimating FFM is most accurate in subjects between 40-60 kg in weight and become less when less than 40 kg. Using the predictive performance plot data provided in this manuscript, the following criteria will be used for calculation of IBW or LBW.

If patient's predicted FFM is between 40-60 kg, the model-predicted FFM should be used for the IBW.

If patient's predicted FFM is between 30-40 kg and BMI is > 25 kg/m², then add 5 kg to the model-predicted FFM to yield the IBW

If patient's predicted FFM is between 30-40 kg and BMI is <25 kg/m², use the patient's actual body weight.

A calculator link (double click paperclip icon to open link) is provided to aid in the calculation of the BMI and FFM values. Users enter patient's height (in), actual bodyweight (kg) and gender will be able to get the respective BMI and predicted FFM value.

In the event that dose rounding is needed in the preparation of the initial dose, the final dose should not exceed a change of 5% from the original calculated dose.

3. Dose Modification During Treatment

Subsequent doses should be escalated or reduced based on toxicity. The dose modification should be based on a percentage escalation or reduction as indicated in the protocol. Patients will be weighed prior to initiation of a new cycle of treatment. Dose recalculation based on weight change must be done if the patient experiences 10% or more weight gain or weight loss from the **last dosing weight**.

II. CALCULATING CREATININE CLEARANCE

1. Background

Because of the general consensus that 24-hour urine collection to determine the glomerular filtration rate (GFR) is difficult to obtain resulting in inaccurate measurement, a suitable calculated creatinine clearance using patient characteristics of age, weight, gender and serum creatinine as surrogates for the clearance-defined GFR is needed. The Cockcroft and Gault method has been the most commonly used.

There has been a great deal of controversy surrounding the limits to be used for serum creatinine. For the purpose of consistency with other professional organization guidelines, the minimum value of 0.8-7 mg/dl has been chosen.

The definition of obesity has also been changing, with ranges of 120%-140% of ideal body weight as a base. A weight no greater than 140% of IBW has been selected for consistency

of calculations.

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2. Procedure

Use the Cockcroft and Gault method to calculate estimated creatinine clearance:

$$\text{CrCl} = \frac{(140 - \text{age}) \times \text{wt. in kg}^\dagger \times 1.00 \text{ (male) OR } 0.85 \text{ (female)}}{72 \times \text{serum creatinine}^*}$$

[†]The kilogram weight is the patient weight with an upper limit of 140% of the IBW.

*Actual lab serum creatinine value with a minimum of 0.8-7 mg/dl.

The MAXIMUM CrCl that can be used based on the Cockcroft and Gault method estimation should be 125 ml/min.

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~~If the estimated CrCl will be used for AUC carboplatin dosing calculations, be aware that per SWOG Protocol Department "Action Letter related to AUC dosing of carboplatin" dated 10/11/2010, the MAXIMUM CrCl that can be used is 125 ml/min~~

In recognition that many site investigators may be required to use their institutional-specific medical record software management system (e.g. Epic Systems) for patient information, SWOG investigators are permitted to use the system-provided calculator to estimate creatinine clearance of study subjects. However, SWOG investigators may also be strongly encouraged to use the online calculator provided by SWOG Statistical Center available in the "Tools of the Trade" section of the CRA Workbench on the SWOG Member website.