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

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RESEARCH CALCULATIONS FOR CLINICAL TRIALS

In recognition that many site investigators may use their institutional-specific medical record software management system (e.g. EPIC Systems) or institutional guidelines for dosing calculations, which may cause variability in the final results leading to protocol violation and/or patient safety issues, the following guidelines are provided. To bring consistency to the conduct of SWOG clinical trials it is recommended that investigators use the online calculators provided by SWOG Statistical and Data Management Center available in the "Tools of the Trade" sectionof the CRA Workbench on the SWOG Member website for drug and end organ function assessments in both patient eligibility determination and post-enrollment to ensure compliance with SWOG policy #38.

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 $\geq$ 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 el. J Clin Oncol 1996;14(11):3000-8, Meyerharsdt, et al. Journalof Clinical Oncology 2004;22(4):648-57, Barrett, et al. Annal 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 dosesbe 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.

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

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 amodel that incorporated gender, height, and bodyweight to predict fat-free mass (FFM). Usingthe 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/m^2. 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/m^2, 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/m^2, use the patient's actual body weight.

The Tool of the Trade BSA Calculator (https://www.crab.org/research-calculators.html) is set up to accommodate all different variables mentioned in this policy in the calculation of the body surface area.

3. Dose Rounding

In the event that dose rounding is needed in the preparation of the study drug, the final dose should not exceed a change of ±5% from the original calculated dose for best practice model. The maximum limit **must** not exceed ±10% to avoid major protocol violation as defined by SWOG and NCI. Dose rounding based on the drug vial size must be in accordance to the maximum limit of 10%.

4. Dose Modification During Treatment

Subsequent doses should be escalated or reduced based on toxicity. Dose modification should be based on the criterion listed in Section 7 and 8 of 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 orweight loss from the **last body weight used for dosing calculation**.

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 0.7 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.

2. Procedure

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

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

†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 0.7 mg/dl.

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

Calculated Creatinine Clearance Formula and Calculator:
https://txwb.crab.org/TXWB/CreatinineClearanceCalculator.aspx