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DOSING PRINCIPLES FOR PATIENTS ON CLINICAL TRIALS

I. TREATMENT DOSING BASED ON BODY SURFACE AREA

1. Background

Body surface area (BSA) is estimated as a mathematical function of height and weight. BSA was first described by Pinkel in 1958 and later by Freireich, et al. in 1966 to allow for extrapolation of drug dosing from lower mammals to humans. The investigator's original goal was to define a safe starting dose for Phase I trials of new anticancer agents. 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.

It has been suggested that the best correlation to drug clearance is lean body mass (LBM), rather than BSA. However, there is no standard method to determine LBM, which is correlated with height, weight, and age. In addition, other important factors such as individual variability that can influence the pharmacokinetic and pharmacodynamics of the drug metabolism are certainly not being taken into account for LBW-based drug dosing.

Upon review of current literature, it is generally agreed that drug plasma level monitoring or the area under the curve (AUC) estimation is the most accurate method of performing individualized dosing calculation at the initiation of therapy. However, this method is very costly and impractical to apply. The use of body surface area as a means of dose calculation appears to be most appropriate at this time. However, the use of ideal versus actual body weight in determining the BSA, especially in obese patients, remains controversial. Some of these studies evaluated patients up to 140% of their ideal body weight (IBW) and found no associated increase of toxicity. A study by Georgiadis, et al. in 1995 treated 262 patients with small cell lung cancer based on their actual body weight. Patients were treated with etoposide plus cisplatin. There were no consistent association of significance found between increasing body mass index (BMI) or BMI levels (normal, obese-120% IBW, and severely obese-140% IBW) and increasing toxicity from therapy. No statistically significant differences were found between the survival of patients within the different BMI levels. The authors concluded that no support for empiric chemotherapy dose reductions based on ideal body weight was evident from this study. A study published in the Journal of Clinical Oncology by Rosner, et al. in 1996 studied 1,435 breast female patients with 568 (40%) obese patients (161% \pm 28% IBW) and 241 (17%) very obese patients (183% \pm 28% of IBW). These patients were treated with CAF doses by their actual weight (within 5%). The obese patients did not experience increase in toxicity or worse outcome as compared to the non-obese patients. The authors recommended initial dose of CAF be computed according to actual body weight. Several recent published studies continued to support the findings of the previous studies use of actual body weight in dosing chemotherapy for the obese patients (defined as BMI \geq 30), especially in the adjuvant setting where the treatment intent is curative. These studies showed that obese patients do not have poorer prognosis if they are treated with optimal doses of chemotherapy based on actual body weight and no increased toxicity was observed (Barrett, et al. Annals of Oncology 2008;19(5): 898-902, Meyerhardsdt, et al. Journal of Clinical Oncology 2004;22(4):648-57). A review article (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. 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 surface area should always be used while calculating the treatment doses. Body surface area can be determined from weight and height by using a nomogram found in standard references. (The Cancer Therapy Evaluation Program has decided not to direct which formula is to be used for BSA-based dose calculation in NCI-sponsored treatment trials.)

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)

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. 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 more than 10 lbs. weight gain or weight loss from baseline. This will be done prior to any further dosing.

II. CALCULATING CREATININE CLEARANCE

1. Background

Because of the issues related to the collection of a creatinine clearance, a suitable calculated creatinine clearance using patient characteristics of age, weight, gender and serum creatinine as surrogates for the clearance-defined glomerular filtration rate (GFR) is needed. With the number of various methods to calculate GFR, all having related problems, the Cockcroft and Gault method has been the most commonly used method.

There has been a great deal of controversy surrounding the limits to be used for serum creatinine. For the purpose of consistency, the minimum value of 0.8 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

Using the Cockcroft and Gault method of calculation of creatinine clearance:

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

[†]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 0.8 mg/dl. For serum creatinine value less 0.8 mg/dl, at least a 6-hour urine collection within 72 hours before treatment is recommended.