Dosing Antineoplastic Medications in Obese Patients

6

Brandon R. Shank

Outline

Introduction

Obesity causes about 20% of all cancers.[1] It is known that adipose tissue secretes excessive amounts of estrogen, increasing patients' risk for breast cancer, especially in postmenopausal women.[2] A high-caloric diet and physical inactivity put individuals at an increased risk of colorectal cancer. Elevated body weight has been associated with an increase in mortality from the following cancers: esophagus, colon, rectal, liver, gallbladder, pancreas, kidney, non-Hodgkin lymphoma (NHL), and multiple myeloma.[3] Challenges in nonpharmacologic interventions in obese patients include the inability to achieve negative margins during surgery, difficulty with optimal positioning of patients during radiation, and achieving deep enough radiation penetration to the tumor.[2] This chapter will discuss disease-specific and antineoplastic medications data in relation to obese individuals.

In addition to the challenges seen with surgical and radiation management of obese patients with cancer, there are significant challenges with delivering adequate concentrations of antineoplastic medications to the tumor. Most antineoplastic drugs have a narrow therapeutic window so achieving the appropriate concentration is paramount. Many chemotherapy agents exhibit dose-dependent cytotoxic activity in vitro.[4] High-dose therapy has been shown to decrease the emergence of resistant malignant clones.[5] Delivering too small of a dose has translated into decreased

efficacy in breast cancer patients and other types of cancer.[6] However, administration of too large a dose has the potential to cause excessive toxicity. Consider the following when determining an antineoplastic drug dose:

Treatment intent—Be aggressive when treating patients for curative intent. Careful consideration should be made when dosing patients for palliation to maximize the patient's quality of life so dose decreases may be warranted.

Weight assessment—Clinically evaluate patients and determine if their body composition is mostly muscle mass or body fat. For example, a body builder may appear overweight on paper but have a significant proportion of lean muscle mass in person. Excess fluid accumulation, such as that seen in ascites, should be assessed as certain drugs (such as methotrexate) can distribute into third-space fluids and cause greater toxicity. Most often total body weight (TBW) is used in the body surface area (BSA) calculation; however, some protocols use an adjusted body weight.

End-organ function—Many antineoplastic agents undergo hepatic or renal clearance. Hepatic flow may be decreased in patients with fatty liver disease, but some studies have shown increases in phase II conjugation reactions in this disease state.[7] For renally cleared medications, adjustments in weight may need to be made to prevent overestimation of the patient's creatinine clearance. See Chapter 1: Introduction to Dosing Medications in Obese Patients for a complete discussion of hepatic and renal changes in obese patients.

Performance status—Patients' performance status can be used as a surrogate for their reserve and ability to tolerate treatment. Patients who are heavily pretreated or have significant comorbidities may not be able to tolerate as intensive treatment.

Determining Body Surface Area

Area under the curve (AUC) is a measure of drug exposure, which is directly related to response and toxicity for many antineoplastic medications. With the narrow therapeutic window of most antineoplastic agents, the goal in drug dosing is to achieve a certain AUC. One of the most significant challenges associated with obtaining the desired AUC is the difference in tumor penetration, due to chemical properties such as lipophilicity and protein binding, of specific agents.

An initial method to mimic AUC estimates is use of BSA that is most commonly used to dose antineoplastic medications. BSA was selected because it closely resembles cardiac output; thus, blood flow to the liver and kidneys where most medications are metabolized and eliminated. BSA allows scientists to easily extrapolate dosing from animals to humans. Some limitations to BSA dosing are that it does not account for body composition, end-organ function changes with age, impact of comorbidities, or sex-related differences.[8]

There are many different formulas to calculate BSA. Consensus opinion is that no formula performs better than another across a wide range of patients.[9,10] Du Bois and Du Bois published the first BSA equation (**Equation 6-1, Table 6-1**) developed from nine individuals of various sizes, including one child and one obese patient (BMI 41.5 kg/m^2).[11] The Du Bois and Du Bois equation has been extensively validated. See **Table 6-1** for a table of available BSA equations. About two decades later, Boyd devised a new, more complex formula from 1,114 individuals (**Equation 6-2, Table 6-1**).[12] The Boyd formula was more accurate for determining BSA in infants and children.

Gehan and George worked to optimize the coefficients of the Du Bois and Du Bois equation, which was done by increasing the sample size (**Equation 6-3, Table 6-1**).[13] The impact