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Review

Impact of obesity on chemotherapy management and outcomes in women with gynecologic malignancies

Neil S. Horowitz [a,b,1], Alexi A. Wright [b]

[a] Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Brigham and Women's Hospital, USA
[b] Division of Medical Oncology, Dana Farber Cancer Institute, USA

HIGHLIGHTS

- Obesity is associated with an increased risk of developing cancer and worse outcomes.
- Up to 40% of obese patients receive inappropriate low doses of chemotherapy.
- Full dose chemotherapy in obese patients does not lead to increased toxicities.
- Guidelines exist that outline appropriate chemotherapy dosing in obese patients.

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ABSTRACT

Objective. To describe the effects of obesity on the pharmacokinetics and dosing of chemotherapies and provide recommendations for chemotherapy management in obese women with gynecologic malignancies.

Methods. PubMEd and MEDLINE databases were searched for articles published before June 2014. Only English-language articles were considered. 84 manuscripts were reviewed and 66 were included. Search terms included: obesity, overweight, body mass index, body surface area, glomerular filtration rate, chemotherapy, ovarian cancer, endometrial cancer, inflammation, and pharmacokinetics,

Results. Obese cancer patients have worse clinical outcomes, compared with non-obese patients. This may be because of differences in pharmacokinetics, metabolic dysregulation, or physicians' decisions to reduce chemotherapy dose-intensity during treatment to minimize toxicities. A 2012 American Society of Clinical Oncology Clinical Practice Guideline recommends using actual body weight for chemotherapy dosing in all patients treated with curative intent, irrespective of obesity, to avoid compromising clinical outcomes, including progression free survival (PFS) and overall survival (OS). In women with gynecologic cancers most studies demonstrate no difference in PFS or OS when obese patients receive the same chemotherapy dose intensity as non-obese patients, except perhaps with bevacizumab.

Conclusions. Chemotherapy dose-intensity is a critical determinant of cancer outcomes and should be maintained in all patients, irrespective of obesity. Future studies should prospectively examine the impact of obesity on clinical outcomes (adverse events, survival) to improve the care of this growing population of patients who are at risk for inferior clinical outcomes.

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E-mail address: nhorowitz@partners.org (N.S. Horowitz).
[1] Contact Information: Division of Gynecologic Oncology, Department of OB/GYN, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115, USA. Tel.: +1 617 732 8843; fax: +1 617 738 5124.

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1. Introduction

Over the past several decades obesity has become a growing epidemic in Western, industrialized nations and the world. In 2005, the World Health Organization (WHO) estimated that by 2030 the number of overweight and obese adults would be 1.6 billion and 400 million, respectively [1,2]. At the current pace, nearly 60% of the world's populations will be either overweight or obese by 2030. In the United States, 60% of the population is overweight and 30% is obese already [3,4]. The implications of this epidemic on U.S. and global populations are enormous as obesity has been linked to coronary heart disease, hypertension, cerebrovascular events, type II diabetes mellitus, osteoarthritis, and depression [5]. Additionally, obesity is associated with an increased risk of developing cancer and worse outcomes for a variety of malignancies, including: breast, gastrointestinal, prostate, pancreas, kidney, bladder, uterus, cervix, and ovary [6–8]. The increased risk of cancer incidence and mortality is multi-factorial, but likely related to both the innate pro-inflammatory/growth dysregulation environment associated with obesity as well as physician biases in the management of malignancies in obese patients.

The aim of this review is to provide a better understanding of the links between obesity and cancer, to discuss the effect of obesity on the pharmacokinetics and dosing of chemotherapies, and to provide specific guidelines on chemotherapy management in obese women with gynecologic malignancies.

2. Measurements of obesity

The direct quantification of body fat is difficult to do and relies on methods that are not readily available in clinical practice. Use of underwater weighing, skin fold measurements, bioelectrical impedance analysis (BIA), or dual energy X-ray absorptiometry (DEXA) can precisely determine a patient's body composition but is impractical for day-to-day clinical practice. As such, in order to describe a patient's weight we use indirect characteristics such as height, weight, age, and gender to calculate various measures of weight/body composition. By far the most common of these is body mass index (BMI) which is calculated by dividing total body weight (TBW) in kilograms (kg) by the square of height in meters (m^2). Using BMI, the WHO has classified overweight as a BMI of 25–29.9 kg/m^2 and obese as a BMI ≥ 30 kg/m^2 (Table 1). Although helpful in defining weight classifications, this categorization does not distinguish between lean muscle mass and adipose tissue.

Table 1
World Health Organization classification of body mass index (BMI).

Classification	Principal cuff-off points for BMI (kg/m^2)
Underweight	<18.50
Severe thinness	<16.00
Moderate thinness	16.00–16.99
Mild thinness	17.00–18.49
Normal range	18.50–24.99
Overweight	≥25.00
Pre-obese	25.00–29.99
Obese	≥30.00
Obese class I	30.00–34.99
Obese class II	35.00–39.99
Obese class III	≥40.00

Patients with the same BMI can have vastly different sizes, shapes, and body compositions. Other calculations such as ideal body weight (IBW), adjusted body weight (ABW), and lean body weight (LBW) incorporate gender and other factors to overcome the shortcomings of BMI.

In oncology the other major body composition measurement is body surface area (BSA). Initially proposed by Pinkel in 1958 to define appropriate pediatric doses for 5 different chemotherapies [9], BSA has become the means by which we dose most chemotherapeutic agents in adults [10]. Although this is the most widely accepted way to calculate doses of chemotherapy, there are a variety of different formulas from which to choose. These formulas incorporate height, weight, and a mathematical constant. There are slight variations in BSA (≤10%) depending upon which formula is used, but none are considered superior and all are reasonable per American Society of Clinical Oncology (ASCO) guidelines [11]. Unfortunately, even when using the same formula, the same BSA can result in significant discrepancies in chemotherapy efficacy and toxicity between patients. As a result, some challenge the use of BSA as the ideal method to calculate chemotherapy dose and question if flat fixed dosing or dose banding would provide more standardized outcomes [12,13].

Flat fix dosing is particularly relevant for select chemotherapies, most important of which in gynecologic oncology is carboplatin. Carboplatin dosing is dependent upon glomerular filtration rate (GFR) and dose calculated with the Calvert formula (dose mg = AUC [target area under the plasma concentration curve] × [GFR + 25]) to achieve a targeted AUC. There are multiple different formulas to calculate creatinine clearance as an estimate for GFR (e.g., Cockroft–Gault, Jelliffe, Modified Jelliffe, or Wright) [14–16]. CrCl is often restricted or capped at 125 mL/min so that the carboplatin dose does not exceed AUC × 150 mL/min [11]. All of these formulas include a factor for weight or BSA, except for the Jelliffe formula. In a study by Nagao and colleagues evaluating carboplatin dosing in 253 gynecologic oncology patients, the Jelliffe formula had the greatest bias, compared with other formulas for calculating creatinine clearance, particularly at the extremes of weight. The Jelliffe formula overestimated CrCl in patients with a low BSA and underestimated CrCl for those with a large BSA. The underestimation of CrCl in the obese population ultimately results in inadequate dosing of carboplatin [17]. Although the Jelliffe formula is imprecise and may underestimate chemotherapy doses in obese patients, it was commonly used in Gynecologic Oncology Group trials. Although CrCl can be estimated with any of the existing formulas, since CrCl correlates with BSA, it seems reasonable to avoid the use of the Jelliffe formula in obese patients since it may result in unnecessary dose reductions. Schmitt and colleagues have proposed a unique formula, using cystatin C, an endogenous marker of GFR that has been shown to be an equally valid predictor of individual dosing of carboplatin in underweight, normal weight, and obese patients [18].

3. Pharmacokinetics and obesity

There are very limited data on the impact of obesity on the pharmacokinetics (PK) of chemotherapy and other drugs. This is in part due to the fact that inclusion criteria into phase I trials and PK analyses often exclude patients with significant co-morbidities that are often found in the obese population. To understand the potential impact therefore, one must look at the two most important components of