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

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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.

Keywords

Obesity; Chemotherapy; Dosing; Pharmacokinetics; Ovarian cancer; Endometrial cancer

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Conflict of interest

No conflict of interest.

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 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.

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. 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 ($\text{dose mg} = \text{AUC} [\text{target area under the plasma concentration curve}] \times [\text{GFR} + 25]$) to achieve a targeted AUC. There are multiple different formulas to calculate creatinine clearance as an estimate for GFR (e.g., Cockcroft–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 $\text{AUC} \times 150 \text{ mL/min}$ [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].

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 pharmacokinetics, volume of distribution (Vd) and clearance, and the impact of obesity on each of these.

Vd, measured from plasma, is an estimate of drug distribution into extra vascular tissue or more precisely drug delivery. The Vd is determined by the physical properties of the drug (molecular size, degree of ionization, lipid solubility, and ability to cross membranes) as well as tissue blood flow and plasma protein binding. Not surprising, for lipophilic drugs, obese patients are likely to have higher Vd [19]. Tissue perfusion and cardiac function may be decreased in obese patients thereby decreasing Vd, while plasma protein binding does not seem to be altered by body composition [20–22]. Given the unique properties of each drug and the biologic variability between patients, it is not surprising that obese and non-obese

patients can have significantly different drug plasma concentrations but similar tissue concentrations [23]. Although it is this target tissue concentration that can be correlated with efficacy and toxicity it is quite difficult to measure in clinical practice. This is why we rely so heavily on toxicity as a surrogate for tissue concentration, to make adjustments in doses.

Clearance of chemotherapy is the volume of blood from which drug is completely removed in a given time, a critical component for devising the correct dosages. Unlike V_d , clearance is not affected by the properties of the drug but by patient physiology and, in particular, blood flow to/through the organ responsible for its extraction. For most drugs, the liver is the primary organ involved in clearing drug from circulation. For obese patients, fat can accumulate in the liver, altering blood flow through the liver, and decreasing clearance [24]. The other organ important for chemotherapy clearance is the kidney. Clearance through the kidney is dependent upon the glomerular filtration rate (GFR) and tubular excretion/reabsorption. Retrospective studies have shown that for obese patients, creatinine clearance, an estimate of GFR, has been shown to be increased, decreased, or similar to non-obese patients [19]. Despite this inconsistency, obese individuals tend to exhibit higher absolute drug clearance, compared with non-obese patients, since clearance correlates linearly with lean body mass and obese patients have a higher total lean body weight, compared with non-obese individuals, although they have a lower lean body weight/total weight overall [25]. In sum, clearance is not linearly correlated with total body weight.

Pharmacokinetic studies in obese women are quite limited but it seems that obesity alters the pharmacokinetics in some, but not all, chemotherapies. Sparreboom et al. [26] conducted a pharmacokinetic study on several chemotherapies in a sub-set of patients. They analyzed the data in two cohorts, lean ($< 25 \text{ kg/m}^2$) and obese ($> 30 \text{ kg/m}^2$). They observed a trend toward higher absolute clearance in obese patients for each of the drugs tested, including cisplatin and paclitaxel. Additionally, they observed a higher V_d in obese patients for drugs including doxorubicin, carboplatin, and paclitaxel, although the difference was not statistically significant. Given this variability in pharmacokinetics in obese patients, using standard pharmacokinetic data is difficult for establishing adequate dosing in obese patients. To overcome this variability newer methods are being developed to establish the correct dose for chemotherapy agents. Therapeutic drug monitoring (TDM) and target concentration intervention (TCI) [27,28] use information about drug and metabolite exposure, age, weight, serum creatinine, hepatic/renal function, and drug-drug interactions to predict drug exposure and individualize doses from cycle to cycle [29]. TDM and TCI can improve efficacy, while minimizing toxicity, but adoption of these methods has proved difficult. For example, TCI requires the ability to analyze drug plasma concentrations early and accurately, which is difficult to do outside of research settings. Although growing, there are limited data available that correlate drug concentration/exposure to clinical outcome, questioning the importance of this factor. A final hurdle is the common use of combination chemotherapy regimens to treat the majority of cancers which make establishing therapeutic ranges for individual drugs difficult.

Cancer and obesity

As mentioned earlier, obesity has been associated with a variety of cancers [6,7]. The increased incidence of malignancies in obese patients is, unfortunately, also associated with reduced progression free (PFS) and overall survival (OS). The reasons for poorer outcomes are unknown, but are likely multi-factorial. Obesity is associated with metabolic dysregulation leading to increased circulation of insulin, IGF-1, adipokines, cytokines, and pro-angiogenic factors. The obesity-associated metabolic conditions can lead to the conversion of monocytes to tumor-associated macrophages and the development of stem cell like properties. These factors are critical regulators of cell growth, neo-vascularity, inflammation, and proliferation of tumor initiating cells, all of which promote cancer development and progression [30,31], and may create the potential for the development of chemoresistance and poor responses to chemotherapy [31]. Obesity also may hamper surgery and make administration of radiotherapy quite challenging both of which can also impact clinical outcomes. In addition to these innate biologic perturbations that result in potentially more aggressive tumors, there is evidence that many clinicians under dose chemotherapy in obese women, to minimize toxicities; e.g., by using ideal body weights instead of total/actual body weight, capping BSA to 2m², or increasing the interval between treatments [11]. Unnecessary reductions in chemotherapy dosing may partially explain the worse clinical outcomes observed in obese populations. These chemotherapy related factors are the primary focus of the remainder of this review.

Chemotherapy and obesity

Retrospective and prospective studies have consistently shown that chemotherapy dose intensity is directly related to clinical efficacy, toxicity, and survival [32,33]. For most drugs, the dose–response curve is quite steep and dose reductions as little as 20% can result in decreased remission and cure rates [34,35]. The improved outcomes observed with increased dose intensity likely relate to limiting the opportunity for tumor re-growth and reductions in the number of and development of resistant clones [36]. Maintaining dose intensity is important enough that some have suggested that monitoring optimal dose delivery should be a measure of the quality of cancer care [37,38]. Despite the importance of maintaining chemotherapy dose intensity, up to 40% of obese patients receive limited chemotherapy doses [11], similar to other at-risk populations (e.g., elderly, patients with significant medical comorbidities). Given the lack of prospective randomized trials evaluating chemotherapy dosing in obese patients, there are considerable variations and uncertainties in chemotherapy dosing in clinical practice [39].

In one observational study in US women diagnosed with early stage breast cancer who were receiving adjuvant chemotherapy progressive dose reductions were delivered with increasing BMI [40]. Although well intentioned, concerns about increased toxicities with full dosing of chemotherapy in obese patients are unfounded, particularly in the adjuvant setting where they may compromise cure rates. Despite the difficulties of reporting toxicities in clinical trials, multiple studies show that obese women treated with chemotherapy based on actual body weight do not experience more short-term or long-term toxicities compared with normal/healthy weight individuals [11,41–48]. In fact, retrospective analyses have

shown that rates of myelosuppression are the same or less pronounced in the obese versus non-obese populations and there are fewer instances of febrile neutropenia with increasing BMI [42,44,49]. Based on the available data, delivering decreased chemotherapy doses to obese patients simply to avoid adverse side effects is unwarranted and potentially harmful.

ASCO guidelines

Given the variability in chemotherapy prescribing practices in obese patients, the common misconceptions about higher rates of chemotherapy toxicities in the obese population, and the absence of clinical trials in this population to define correct dosages, ASCO published a clinical practice guideline in 2012 outlining appropriate chemotherapy dosing in obese adult patients with cancer [11]. A panel of experts in medical and gynecologic oncology, clinical pharmacology, pharmacokinetics and pharmacogenetics, and biostatistics conducted a systematic literature review (predominately in breast, ovarian, colon, and lung cancers) and issued guidelines to answer clinical questions that concern the management of obese patients with cancer. These questions focused on the effect of full weight-based dosing of chemotherapy on clinical toxicities and outcomes, the management of high grade toxicities in obese patients, the use of BSA-based and fixed dose chemotherapy calculations, and the role of pharmacokinetics and pharmacogenetics in determining the optimal chemotherapy dose in obese patients. A summary of these guidelines are presented in Table 2. Although data for the morbidly obese (BMI ≥ 40 kg/m²) are extremely rare, the same recommendations outlined for the obese were also proposed for the morbidly obese. Unfortunately there are limited data available regarding appropriate dosing of biologic and targeted chemotherapy agents in obese patients. The ASCO guidelines did not address dosing of these agents, and few studies have examined the pharmacokinetics and distribution of biological chemotherapy in the obese population since this publication.

Disease specific data

The impact of obesity on ovarian cancer outcomes and chemotherapy dosing has been evaluated in several studies with conflicting results (Table 3). While some studies suggest that obesity is a negative prognostic factor, which has been associated with a shorter time to recurrence and shorter overall survival [50–52], others have shown that there is no difference in survival between obese and non-obese women when rates of optimal cytoreduction are equivalent and women receive appropriate doses of chemotherapy [53,54]. As with other diseases there is mounting evidence that dose-dense chemotherapy is associated with significant improvements in survival for women with ovarian cancer [55]. Maintaining dose intensity in obese women can be challenging because of the use of dose capping to avoid clinical toxicities or the Jelliffe formula to estimate CrCl when calculating carboplatin dosing. In an ancillary analysis of Gynecologic Oncology Group trial #158, which used the Jelliffe formula for carboplatin dosing, Wright et al., showed that obese patients had a lower relative decrease in platelet counts and hemoglobin with the first treatment cycle, compared with normal and overweight patients. These trends continued over the entire treatment course. Although there was no statistically significant difference in PFS or OS across BMI strata, there was a trend toward increased risk of disease progression in obese patients [56]. The authors hypothesized this observed difference in toxicity and

disease progression may have been the result of under-dosing of carboplatin with the use of Jelliffe formula. Despite using the Cockcroft–Gault equation in the calculation of carboplatin dosing, similar results were seen in a retrospective review of carboplatin and paclitaxel dosing in the Australian Ovarian Cancer Study [57]. For the obese women in this cohort, 32% received sub-optimal paclitaxel doses and were more likely to receive <85% of relative dose intensity (RDI) of carboplatin. Patients receiving <85% of RDI had a trend toward poorer PFS compared with those receiving >85%, but this was not significant after controlling for known prognostic factors in a multivariable analysis. The authors did not address toxicity in this review. In contrast, a retrospective analysis of the Scottish Randomized Trial in Ovarian Cancer (SCOTROC) I study [53], in which obese patients received the same chemotherapy dose intensity as non-obese patients, there was no difference in PFS or OS between obese and non-obese populations. This difference is likely the result of more accurate dose calculations (i.e. estimations of GFR and BSA capping were not used). Before study entry, all patients had a measurement of GFR by plasma clearance of EDTA, 99mTc-DTPA, or 24-hour urine collection so estimations of GFR were not permitted. In addition, no dose capping was allowed for taxanes. The toxicity findings from the Wright et al. [56], study were also challenged by the results of a single institutional study evaluating chemotherapy dosing in women with ovarian and endometrial cancer. Schwartz et al., [49] compared the toxicities and dose modifications seen in women with a BSA > 2 m² using uncapped versus capped paclitaxel dosing received during adjuvant therapy with carboplatin and paclitaxel. The Jelliffe equation was used to dose carboplatin in both groups. When chemotherapy was dosed using actual bodyweight and not capped, there were no statistically significant differences in rates of hematologic or gastrointestinal toxicities, febrile neutropenia, or peripheral neuropathy, and there were no differences in paclitaxel dose delays, reductions, or discontinuations. Taken together these studies highlight the need to maintain chemotherapy dose intensity by ensuring accurate GFR estimation or actual measurement, using actual body weight for BSA dose calculations, and avoiding chemotherapy dose capping.

Newer data has demonstrated that the addition of bevacizumab to carboplatin and paclitaxel chemotherapy for the primary treatment of ovarian cancer or platinum-sensitive recurrent ovarian cancer results in statistically significant improvements in PFS [58–60]. Unfortunately there are few indicators to predict who will benefit from anti-angiogenic therapy. Increased levels of VEGF, the primary target of bevacizumab and the key regulator of angiogenesis, are associated with obesity. However, existing data regarding the influence of obesity on outcomes of patients treated with anti-angiogenic therapy are controversial. In patients with metastatic colorectal carcinoma, treatment with chemotherapy regimens containing bevacizumab resulted in poorer response rates and shorter PFS and OS in obese patients, compared with chemotherapy regimens without bevacizumab [61]. Additionally, in an ancillary analysis of CAIRO and CAIRO2 study of patients with advanced colorectal cancer, BMI was an independent prognostic factor for prolonged survival when treatment consisted of standard chemotherapy, but not when chemotherapy included bevacizumab [62]. Conversely, for those with metastatic renal cell carcinoma, obesity has been associated with improved outcomes in patients treated with anti-angiogenic therapy [63]. The effect of obesity on outcomes of women with ovarian cancer treated with bevacizumab has not been

well studied. In a review of 46 patients with ovarian cancer, Slaughter et al. found that patients with high levels of adiposity (measured by BMI, sub-cutaneous fat area, and visceral fat area), may not derive the same benefits from bevacizumab as those with lower levels, and levels of adiposity may be a biomarker for predicting response to anti-angiogenic therapy [64].

The impact of obesity on chemotherapy dosing and clinical outcomes in women with endometrial cancer is less well studied. In an ancillary review of GOG-99, women with BMI 40 (morbid obesity) had higher rates of recurrence and decreased survival (HR = 2.77, $p = 0.016$), compared with patients who were not morbidly obese, although approximately 70% of the deaths were from non-cancerous causes. In another study of adjuvant radiation, increased BMI was protective against gastro-intestinal toxicities but was associated with increased cutaneous toxicities [65]. As far as the impact of obesity on chemotherapy, Modesitt and colleagues analyzed data from several randomized GOG trials (GOG trial #107, 122, 139, 163, and 177), all of which had at least one arm evaluating cisplatin and doxorubicin. In the pooled analysis of approximately 950 patients, 33% were obese and 10% were morbidly obese. Increasing BMI was associated with a significantly increased risk of death in patients with Stage III/IV disease (HR = 1.86, $p = 0.010$) and significantly lower rates of Grade 3 and 4 toxicities, particularly in those who were treated with capped dosing [66].

Conclusion

Caring for obese women with cancer can be particularly challenging. Overcoming the inherent mechanisms by which obesity drives cancer progression and increases the risks for worse outcomes will take a coordinated and focused effort by everyone involved in treating these patients. Although encouraging good nutrition, weight loss, and physical activity to prevent the development of cancer and potentially improve cancer outcomes are important future interventions worth investigating, we must ensure that that we understand the impact of obesity on the management of those with known cancers now. Specifically, existing data suggests that obese patients are at risk for receiving substandard care, including unnecessary reduced chemotherapy dose intensity, which may compromise their progression free and overall survival unnecessarily. Existing clinical guidelines suggest that chemotherapy dosing should be calculated based upon body surface area using actual weight, instead of an estimate or idealization of body weight [11]. Future studies should prospectively examine the pharmacokinetics and distribution of biological agents and targeted therapies in obese populations to improve the care of this growing population of patients who are at risk for inferior clinical outcomes.

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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

Table 2

Summary of American Society of Clinical Oncology Clinical Practice Guidelines for chemotherapy dosing in obese patients.

Clinical question	Recommendation
Is there evidence that full weight-based dosing increases toxicity in obese patients with cancer?	<ul style="list-style-type: none"> ● No evidence that short or long term toxicity is increased ● Use actual body weight
Is there evidence that less than full weight-based dosing compromises efficacy in obese patients with cancer?	<ul style="list-style-type: none"> ● Reduced doses can result in worse progression free survival (PFS) and overall survival (OS) and higher recurrence rates. ● Use full weight-based dosing, particularly for treatment for curative intent.
If an obese patient experiences high grade toxicity should it be managed differently than in a non-obese patients with cancer?	<ul style="list-style-type: none"> ● Dose reductions and schedule modifications should be the same regardless of weight ● Changes should be based on the type and severity of the toxicity, comorbidities, and intent of therapy (curative vs. palliative)
Is the use of fixed dose (prescribed independently of weight or BSA) ever justified?	<ul style="list-style-type: none"> ● Only recommended with selected agents (carboplatin, bleomycin, vincristine)
How should BSA be calculated?	<ul style="list-style-type: none"> ● Any standard formula can be used
What is the role of pharmacokinetics and pharmacogenetics on determining optimal dose and delivery of chemotherapy in obese patients with cancer.	<ul style="list-style-type: none"> ● Further research is necessary given limited available data ● No pharmacokinetic data would suggest that the recommendation to use full weight-based dosing should be rejected

Table 3

Published clinical trials evaluating the impact of obesity on surgical outcome and survival.

Study	PFS (months)		OS (months)		% Optimal cytoreduction		Chemotherapy dosing
	Obese	Non-obese	Obese	Non-obese	Obese	Non-obese	
Mathews (n = 304) [†]	17.0	11.0	48.0	40.0	52.0	51.0	ABW, BSA capped
Slaughter (n = 46)							
Chemotherapy [†]	17.6	11.9	48.7	19.5	NR	NR	NR
Bevacizumab [*]	9.8	24.7	44.9	34.1			
Barrett (n = 1067) [†]	16.6	14.7	34.3	30.1	40.0	31.0	ABW, GFR calculated
Au-Yeung (n = 333) [†]	14.0	13.0	43.0	41.0	59.0	54.0	BSA and CrCl capped

Abbreviations: PFS = progression free survival, OS = overall survival, ABW = actual bodyweight, BSA = body surface area, NR = not reported; GFR = glomerular filtration rate; CrCl = creatinine clearance.

[†] P-value 0.05.

^{*} P-value for PFS 0.03 and OS 0.06.