Gynecologic Oncology 138 (2015) 154–158

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

# The effect of weight-based chemotherapy dosing in a cohort of gynecologic oncology patients

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## HIGHLIGHTS

- No serous effects were noted in obese patients who received full weight- based dosing
- Heme toxicities were not seen in obese patients with capped vs weight-based dosing
- Weight-based dosing in gynecologic oncology patients appears to be well tolerated

## ARTICLE INFO

*Article history:*
Received 20 February 2015
Accepted 29 April 2015
Available online 6 May 2015

*Keywords:*
Chemotherapy
Dosing
Obesity
Toxicity

## ABSTRACT

*Objective.* Many clinicians limit chemotherapy doses based on a maximum body surface area (BSA) of 2 $m^2$. We sought to determine how chemotherapy-related toxicities compared between groups of patients that varied with respect to BSA. We hypothesized that obese patients receiving weight-based (WB) dosing would not have significantly higher chemotherapy-related toxicities than control groups.

*Methods.* We performed a retrospective review of patients with BSA ≥ 2 $m^2$ who received WB chemotherapy for a gynecologic cancer between January and August 2013. Subjects were matched with two controls: patients with BSA < 2 $m^2$ who received WB dosing, and patients with BSA ≥ 2 $m^2$ who received capped dosing at BSA = 2 $m^2$. Groups were matched for medical co-morbidities and prior cancer treatment. Demographic and clinical information was extracted and analyzed via ANOVA and Fisher's exact test.

*Results.* A total of 75 patients were included. The three groups were similar in their medical co-morbidities and prior cancer treatment. When comparing pre- and post-treatment laboratory values, there was no difference in hematologic toxicities. There was no difference between groups with regard to treatment delays, unplanned admissions, transfusions, or dose reductions for toxicity.

*Conclusions.* Gynecologic cancer patients with BSA ≥ 2 $m^2$ treated with WB chemotherapy had no increase in hematologic or non-hematologic toxicities when compared to controls. Consideration should be given to using WB dosing in obese patients with gynecologic malignancies. Further investigation is required to determine the effect of WB dosing on progression-free and overall survival in obese gynecologic cancer patients.



## 1. Introduction

Obesity is a known risk factor for cancer at multiple sites, including the endometrium, breast, colon, kidney and gallbladder. Obese patients with cancer have been demonstrated to have higher rates of death than patients with normal body weight [1]. The incidence of obesity in the United States is increasing. Recent data estimates that more than two thirds of adults in the United States are overweight or obese with a body mass index (BMI) greater than 25–30 kg/$m^2$ and that approximately 6% of adults in the United States are morbidly obese with a BMI > 40 kg/$m^2$ [2]. Obesity poses a particular problem for the treatment of patients with cancer for many reasons, one of which is the dosing and administration of chemotherapy. The majority of cytotoxic chemotherapy drugs are dosed according to body surface area (BSA), expressed in meters squared ($m^2$). BSA is a computed number using patient height and weight entered into one of many different formulas. Patients with increased adipose content are thought to metabolize medications differently than normal weight patients. This may be secondary to decreased regional blood flow, decreased cardiac output, altered hepatic drug metabolism secondary to fatty infiltration of the liver, increased levels of plasma proteins leading to decreased free drug levels, or a combination

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http://dx.doi.org/10.1016/j.ygyno.2015.04.040
0090-8258/

of the above [3]. This has led some authors to the conclusion that the increased cancer-related mortality in obese patients may, at least in part, be due to inadequate dosing of chemotherapy [4,5].

Dosing of chemotherapy in obese patients remains controversial, and many clinicians continue to have concerns that weight-based dosing will lead to unacceptable toxicity. This deep-seated practice is perhaps best demonstrated by the fact that Gynecologic Oncology Group (GOG) studies cap doses of many chemotherapeutic agents at a maximum BSA of 2 $m^2$. Furthermore, many institutions have sought to mitigate this problem by using alternate weight computations in place of actual body weight in chemotherapy dose calculations [6]. In order to address both the rising rate of obesity, and the evidence that underdosing of chemotherapy may be leading to worse outcomes in obese patients, the American Society of Clinical Oncology (ASCO) put forth evidence-based guidelines (referred to as ASCO guidelines in this document) that recommend full weight-based dosing of chemotherapy in obese patients [7]. If dose reductions are necessary due to toxicity, it is recommended that full weight-based dosing is resumed as soon as toxicities have resolved. These guidelines identified that as many as 40% of obese patients with cancer may be receiving sub-therapeutic dosing of cytotoxic chemotherapy.

Investigations thus far into the effect of weight-based dosing in gynecologic cancer have yielded similar results. Schwartz et al. demonstrated that there was no increased grade 3 or 4 toxicity when weight-based dosing was used in obese patients with ovarian and endometrial cancer [8]. The SCOTROC I trial showed no link between obesity and worse prognosis in ovarian cancer. These findings were hypothesized to be due to accurate weight-based dosing in this cohort of patients, further supporting the utility of full weight-based dosing [4]. While these studies provide support for the ASCO guidelines, there still is limited evidence evaluating the effect of these guidelines on current clinical practice and patient outcomes, especially in women with gynecologic cancer.

The objective of this study was to determine how weight-based chemotherapy dosing affects adverse drug reactions in obese gynecologic cancer patients at our institution. We hypothesized that full weight-based dosing would not increase adverse drug reactions and could be safely administered to obese patients with gynecologic cancers.

## 2. Methods

Approval was obtained from the University of Iowa Institutional Review Board. All patients at our institution with a body surface area (BSA) greater than or equal to 2 $m^2$ who received weight-based chemotherapy for a gynecologic malignancy between January and August 2013 were reviewed. These subjects were matched with two sets of controls based on chemotherapy agent, prior treatment history, and medical co-morbidities: 1) subjects with a BSA greater than or equal to 2 $m^2$ who received chemotherapy doses capped at a BSA of 2 $m^2$, and 2) subjects with a BSA of less than 2 $m^2$ who received weight-based dosing. Chemotherapy agents analyzed were those dosed according to BSA and included gemcitabine, liposomal doxorubicin and paclitaxel. Demographic data including age, height, weight, BMI and BSA as well as medical co-morbidities, which were grouped by body system, were extracted from the medical record. Disease status, including primary tumor site, stage, histology and grade were noted, as well as data pertaining to each chemotherapy treatment, including agent, dose, cycle, prior chemotherapy history, and prior radiation history. Values for white blood cell count (WBC), absolute neutrophil count (ANC), platelet count, and creatinine were noted. Pre-treatment values were defined as the lab values obtained on the first day of the first cycle of chemotherapy received during the study period. Post-treatment laboratory values were defined as values obtained on the first day of the second cycle during the study period. Differences between the pre- and post-treatment lab values were compared between groups. A thorough review of systems was collected by the provider at each clinic visit during the study period. Symptoms reported by the patient were noted and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events [9]. Adverse chemotherapy-related events, defined as treatment delay, unplanned hospital admission, unplanned blood transfusion, or dose reduction due to toxicity, were noted for each group. A sub-analysis was performed for patients receiving paclitaxel, either alone or in combination with carboplatin, and included an analysis of adverse chemotherapy-related events and laboratory values.

To evaluate group differences in age and BSA, an ANOVA was utilized. Given the repeated measurements of laboratory values and chemotherapy-related events, the mean differences in WBC, ANC, platelets and creatinine were adjusted for multiple measurements per patient. Pairwise comparisons were performed to test for specific differences in the means. Comparisons for differences in the number of patients with treatment delays, admissions, transfusions and dose reductions were also adjusted for repeated measurements. All statistical tests were two-sided and carried out at the 5% level of significance with the SAS software, version 9.2 (Cary, NC).

## 3. Results

A total of 246 cycles of chemotherapy were analyzed, comprised of 82 cycles in each of the three groups detailed in Table 1: BSA < 2 $m^2$ weight-based (N = 82 cycles; 30 patients), BSA ≥ 2 $m^2$ capped (N = 82 cycles; 22 patients), and BSA ≥ 2 $m^2$ weight-based (N = 82 cycles; 23 patients). The two groups with BSA ≥ 2 $m^2$ did not have statistically different body surface areas (p = 0.07). The three groups were however statistically similar in age (p = 0.03), with the BSA < 2 group containing the oldest age patients. The three groups had similar medical comorbidities and all patients had a GOG performance status of 0 or 1. As noted in the table, the majority of chemotherapy cycles were

**Table 1**
Patient characteristics stratified by BSA.

| | BSA < 2 | | BSA ≥ 2 | | BSA ≥ 2 | | |
|---|---|---|---|---|---|---|---|
| | Weight-based | | Capped | | Weight-based | | |
| Variable | N | Mean | N | Mean | N | Mean | p-Value |
| Age (years) | 30 | 64.27 | 22 | 59.82 | 23 | 55.70 | 0.03 |
| BSA ($kg/m^2$)[1] | 30 | 1.77 | 22 | 2.29 | 23 | 2.19 | 0.07 |
| Cancer site | | | Cycles of chemotherapy | | | | Total |
| Ov/FT/PP | 56 | | 48 | | 34 | | 138 |
| Endometrium | 21 | | 29 | | 37 | | 87 |
| Cervix | 5 | | 5 | | 11 | | 21 |
| Agents used | | | Cycles of chemotherapy | | | | |
| Gem (alone) | 3 | | 0 | | 3 | | 6 |
| Gem + platinum | 0 | | 3 | | 0 | | 3 |
| Lipo dox (alone) | 18 | | 11 | | 18 | | 47 |
| Lipo dox + carbo | 1 | | 8 | | 1 | | 10 |
| Paclitaxel (alone) | 4 | | 4 | | 4 | | 12 |
| Paclitaxel + carbo | 56 | | 56 | | 56 | | 168 |
| Prior treatments | | | Cycles of chemotherapy | | | | |
| Chemo only | 26 | | 26 | | 28 | | 80 |
| Chemo + XRT | 13 | | 5 | | 3 | | 21 |
| XRT only | 0 | | 6 | | 6 | | 12 |
| No prior | 43 | | 45 | | 45 | | 133 |

BSA: body surface area.
Ov: ovarian cancer.
FT: fallopian tube cancer.
PP: primary peritoneal cancer.
Gem: gemcitabine.
Platinum: cisplatin.
Lipo dox: liposomal doxorubicin.
Carbo: carboplatin.
XRT: radiation therapy.
[1] Comparisons for BSA were performed for patients with BSA ≥ 2 only.