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ScienceDirect
Gynecologic Oncology 105 (2007) 59–65
Gynecologic Oncology
www.elsevier.com/locate/ygyno

Impact of body mass index on treatment outcomes in endometrial cancer patients receiving doxorubicin and cisplatin: A Gynecologic Oncology Group study

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Received 18 July 2006
Available online 5 December 2006

Abstract

Objectives. To evaluate the association between body mass index (BMI) and outcomes in women with advanced or recurrent endometrial cancer treated with doxorubicin/cisplatin.

Methods. Data from patients treated on five Gynecologic Oncology Group trials were retrospectively reviewed. BMI was categorized as normal (<25), overweight (≥25 to <30), obese (≥30 to <40), and morbidly obese (≥40). BMI was analyzed for associations with demographics, clinical characteristics, toxicity, progression-free survival (PFS), and overall survival (OS).

Results. Among 949 patients, 533 (56%) had recurrent disease, 227 (23.9%) had Stage IV disease, and 189 (19.9%) had Stage III disease. Mean BMI was 29.8; 29.6%, 27.0%, 33.2% and 10.2% of patients, respectively, were categorized as normal, overweight, obese, and morbidly obese. The mean BMI was significantly different when compared by age group ($p<0.001$), stage ($p=0.047$), histologic type ($p=0.024$), and tumor grade ($p=0.014$). Older patients and those with clear cell, poorly differentiated tumors, or stage IV disease had a lower BMI. No significant associations between PFS and BMI were detected. Increasing BMI was significantly associated with an increased risk of death in Stage III/IV (HR=1.86, 95% CI 1.16–2.99 for BMI≥40 vs. BMI<25) but not recurrent patients. Higher BMI patients had less Grade 3/4 toxicities than normal patients ($p<0.001$) but this difference disappeared for obese patients receiving ≥95% of the calculated dose.

Conclusions. BMI was not predictive of PFS in this endometrial cancer population although morbidly obese patients had decreased OS in primary Stage III/IV patients. Toxicities decreased with increasing BMI, perhaps secondary to capped dosing.
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Keywords: Endometrial cancer; Lower uterine segment; Nodal disease; Prognosis

Introduction

Obesity is an increasing health problem in the United States; 65% of the population in the U.S is overweight; moreover, 30% of the population is obese based on body mass index (BMI) [1]. BMI is calculated using the weight (in kg) divided by the square of the height (in meters). The World Health Organization (WHO) defines BMI as normal (BMI 18 to <25), overweight (BMI ≥25 to <30), obese (BMI ≥30), and morbidly obese (BMI ≥40) [2,3]. Cancer remains the second leading cause of death in the developed world behind heart disease and the link between obesity and cancer is becoming more evident. Among reports linking a variety of cancers to obesity, the most consistent and striking finding has been the association between obesity and endometrial carcinoma [3–28]. In the U.S., uterine

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0090-8258/$ - see front matter © 2006 Elsevier Inc. All rights reserved.
doi:10.1016/j.ygyno.2006.10.045

cancer remains the most commonly diagnosed gynecologic malignancy with 41,200 cases estimated in 2006 [29]. The most common cell type is endometrioid adenocarcinoma which appears to be more closely linked to obesity than the more aggressive cell types that often arise in a setting of atrophic endometrium [4,14].

In evaluating the impact of obesity on cancer incidence, Calle et al. asserted that more than 90,000 cancer deaths per year could be avoided in the U.S. if adults maintained a lifelong BMI <25 [10]. Furthermore, they reported significant trends for increased risk of death from cancers of the breast, uterus, cervix, and ovary in women with an elevated BMI. For example, morbidly obese women (BMI ≥40) had a cancer death rate that was 62% higher than that of women with a normal weight [10]. It remains unclear whether the increased mortality among obese women represents an increased incidence of these malignancies, delayed diagnosis, differential treatment, or differential response to treatment compared to their lean counterparts.

In addition to the role obesity plays in the genesis of endometrial cancer, obesity also poses a substantial challenge to cancer treatment. Overweight and obese women face increased surgical morbidity and more difficult radiation dosimetry. There is also ongoing controversy regarding the appropriate chemotherapy dosing paradigm for these patients such that there is currently not a standardized approach to chemotherapy dosing in obese patients. Some national collaborative groups use a predefined maximum dose; for example, the Gynecologic Oncology Group (GOG) routinely caps the body surface area (BSA) dosing at 2 m^2. Although a literature search failed to find dosing data specific for gynecologic cancers, there are reports in breast, lung, and colorectal cancers regarding dosing in obese women. These studies seem to indicate that women should be dosed based on actual body weight to maximize efficacy and that toxicity did not seem to be increased even with dosing on actual body weight [30–36]. One potential hypothesis could be that obese women with gynecologic malignancies should be dosed on actual body weight to prevent potentially lower response rates and inferior outcomes.

The objective of the current study was to evaluate the impact of BMI on treatment toxicity and survival for women with advanced or recurrent endometrial cancer treated with doxorubicin/cisplatin on five randomized GOG trials. A secondary objective was to report the proportion of women whose chemotherapy dosing was capped in GOG protocols and to determine if that was associated with outcomes.

Methods

This was a retrospective review of data from women who participated in one of five prospective, randomized Phase III treatment trials for advanced stage or recurrent endometrial cancer conducted by the Gynecologic Oncology Group (GOG Protocols 107, 122, 139, 163, and 177). Each of these trials was comprised of at least one arm utilizing doxorubicin/cisplatin chemotherapy. Participating institutions' Institutional Review Boards approved the trials prior to enrolling any patients and all patients provided written informed consent consistent with all local, state, and federal requirements before receiving any protocol treatment. Eligibility criteria and treatment details for these studies have previously been described [37–41]. The methods used for surgical staging were consistent for these five protocols. Patients included in this ancillary data analysis had advanced stage (Stage III or IV) or recurrent disease, received doxorubicin/cisplatin chemotherapy, and had height and weight available for calculation of BMI (see Table 1 for details of patient demographics and clinical characteristics by study). BMI was calculated using the weight (in kg) divided by the height squared (in meters). The GOG defined the maximum BSA as 2 m^2.

Demographic and clinical data, along with tumor and treatment-related outcomes were collected. BMI was calculated and patients were categorized as normal (BMI<25), overweight (BMI≥25 to <30), obese (≥30 to <40), and morbidly obese (BMI≥40). An analysis of variance was performed to test the difference in mean BMI across groups with the Tukey–Kramer method utilized for pair-wise comparison. A Cox proportional hazards model was used to assess the impact of BMI classification on both progression-free (PFS) and overall survival (OS) after adjusting for covariates. Kaplan–Meier survival curves based on BMI classification were calculated and compared using the log-rank test. Since the primarily advanced (stage III or IV) and recurrent patients may be biologically different, the assessment of association between BMI and clinical outcome was conducted separately, stratified by advanced patients and recurrent patients. Percentage weight-based chemotherapy dosing was calculated as prescribed: (recorded) cycle 1 dose/expected (BSA dose)×100%. BSA was computed using the DuBois method: BSA (m^2)=0.007184×height (cm)$^{0.725}$×weight (kg)$^{0.425}$. The association of BMI classification with selected toxicities was evaluated using a logistic regression model, adjusted for age, prior radiotherapy, and treatment protocol. For leukopenia, thrombocytopenia, neutropenia, anemia, and gastrointestinal toxicities, we included those meeting the Common Toxicity Criteria (CTC) version 2 for Grade 3 or 4 toxicity; for genitourinary, neurologic, and cardiovascular effects, we included all grades of toxicity. For those patients with BSA >2.0, the initial chemotherapy dose was usually required by the protocol to be calculated using BSA=2.0 (capped dosing). But, in a clinical practice, the physician might or might not follow this capped rule. Thus, for this study, capping was evaluated by comparing the recorded (prescribed) initial dose in the patient's chart to expected (weight-based) dose. For this analysis, capped dosing was defined as less than 95% of expected dose. In patients with BSA >2.0, the survival and selected toxicities were compared between capped and uncapped groups using the same methods as above. All reported p values were two sided and the statistical analyses were performed on Statistical Analysis System (SAS) version 9.1 (SAS Institute, Cary, NC).

Results

A total of 949 eligible patients who were enrolled on GOG 107, 122, 139, 163, and 177 and treated with doxorubicin/

Table 1
GOG treatment protocols and study populations

GOG study	FIGO stage	Treatment regimen	No. of patients eligible
107	Stage III, IV, and recurrent measurable disease	Doxorubicin 60 mg/m^2 Cisplatin 50 mg/m^2	131
122	Stage III and IV <2 cm residual	Doxorubicin 60 mg/m^2 Cisplatin 50 mg/m^2	193
139	Stage III, IV, and recurrent measurable disease	Doxorubicin 60 mg/m^2 over 30 min Cisplatin 60 mg/m^2 over 30 min OR	169
		Doxorubicin 60 mg/m^2 over 30 min at 6 am Cisplatin 60 mg/m^2 over 30 min at 6 pm	171
163	Stage III, IV, and recurrent measurable disease	Doxorubicin 60 mg/m^2 Cisplatin 50 mg/m^2	157
177	Stage III, IV, and recurrent measurable disease	Doxorubicin 60 mg/m^2 day 1 Cisplatin 50 mg/m^2 day 1	128

Initial chemotherapy dosing required to be adjusted approximately for old age and prior radiotherapy for protocols 107, 139, 163, and 177 (detailed information described by references [41–45]).

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