Description of Current Practices of Empiric Chemotherapy Dose Adjustment in Obese Adult Patients

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Abstract

Purpose: The literature is not clear on the best method to empirically dose chemotherapy in obese adult patients. The purpose of our study was to determine whether a standard of practice existed, characterize current practices of empiric dose adjustment (EDA) in obese adult patients, and identify factors affecting this decision.

Methods: An electronic survey was distributed to oncologists and board-certified oncology pharmacists via the Association of Community Cancer Centers and Board of Pharmaceutical Specialties e-mail distribution lists. The survey contained patient scenarios assessing the impact of various factors on EDA of chemotherapy, demographic information, and details of institutional policies.

Results: Responses were collected from 174 professionals. Pharmacists comprised 95% of respondents. Of these, 50% practiced in academic medical centers, and 19% practiced in institutions with a standard of practice regarding EDA for obesity. The most common methods of EDA were use of an adjusted body weight in the body-surface area (BSA) equation and capping BSA. Factors with the most impact on EDA were curative intent, degree of obesity, type of chemotherapy, and performance status.

Conclusion: There is no standard of practice regarding EDA of chemotherapy in obese adult patients. Although many factors affect this decision, intent of treatment, degree of obesity, performance status, age, and type of medication seem to carry the most weight.

Introduction

Obesity has increased to epidemic proportions, with 32.2% of US adults age 20 years or older classified as obese (body mass index ≥ 30 mg/m²).¹ In addition to being associated with development of certain cancers, obesity increases the occurrence of comorbidities (CMs) that may complicate treatment.² Obesity is associated with increased cancer-related mortality; however, it is unclear whether this is a result of CM, tumor biology, treatment, or a combination of these factors.³

Obesity affects chemotherapy pharmacokinetics; obese patients have increased fat percentage per actual body weight (ABW) and altered regional blood flow (a review of obesity effects on pharmacokinetics can be found elsewhere⁴). This affects volume of distribution, clearance, and consequently patient drug exposure. Chemotherapy dosing is typically individualized based on the patient's body surface area (BSA), which helps achieve a predicted drug exposure for a given patient.⁵ BSA calculations and chemotherapy dose recommendations are typically derived from studies excluding obese patients.^{6,7} In many situations, severely obese patients dosed on ABW have increased drug exposure as a result of the altered pharmacokinetic profiles. Clinically, this presents as excessive toxicity. Consequently, dose reductions in obese patients may be justified in some circumstances.

To our knowledge, there are no reports in the literature identifying patients who should have empiric dose adjustment (EDA) because of obesity or the best method of dosing chemotherapy to standardize drug exposure in patients with varying degrees of obesity. We believe clinicians determine the need for EDA on the basis of perceived risk versus benefit. Anecdotally, this includes curability, performance status (PS), number and

type of CM, age, type of therapy (targeted agent *v* cytotoxic), expected toxicity, and degree of obesity.

Once the decision is made to perform EDA for obesity, there is not an accurate best method. A common approach is to adjust the weight on the basis of documented changes in body composition, which is subsequently incorporated into the BSA calculation. It is estimated that 20% to 40% of excess body weight is lean mass, leading to adjusted body weight (AdjBW) calculations that take ideal body weight (IBW) and add 25% or 40% (AdjBW40) of obese weight,^{8,9} but extrapolated data are common. As a result, oncology practitioners employ a variety of EDA methods, such as capping BSA or using alternate weight estimates like IBW, lean body mass, AdjBW, or mean body weight (MBW) in the BSA calculation.⁵ As the incidence of obesity increases, EDA of chemotherapy becomes an issue of growing importance.

Prospective evaluation of EDA in obese adult patients is warranted; however, trials are difficult to design because of the lack of description of current practice. We sought to characterize current practice and identify factors affecting EDA to better design prospective trials. We hypothesized there was no standard for EDA of chemotherapy in obese adults, and EDA would be affected by medication type and patient variables such as curative intent, age, degree of obesity, PS, and CM.

Methods

Population

Our survey was e-mailed in October 2008 to board-certified oncology pharmacists (n = 575) and board-certified medical oncologists who were members of an e-mail distribution list of the Association of Community Cancer Centers (n = 1,000). The survey was anonymous, and no identification numbers were used.

Table 1. Respondent Demographics (n = 174)

Demographic	%
Profession	
Pharmacist	94.7
Physician	5.3
Practice site	
Academic institution	35.6
Private institution	16.7
Government institution	2.3
Managed care organization	3
Inpatient site	17.4
Ambulatory site*	25
Distribution of patient care time, %	
Solid malignancies	
> 75	23.3
25-75	60
≤ 25	16.7
Hematologic malignancies	
> 75	2.2
25-75	53.9
≤ 25	
HSCT	43.8
> 75	5.4
25-75	13.5
≤ 25	81.1

Abbreviation: HSCT, hematopoietic stem-cell transplantation.

* For example, infusion center or outpatient clinic.

Survey Design

The survey sought demographic information and included six fictional patient cases (Appendix, online only) designed to highlight the impact of patient variables and medication properties on EDA. Patient cases were created using cancer diagnoses and chemotherapy common in the United States.^{4,10} The survey was piloted among 12 pharmacists at our institution to gather feedback and increase ease of administration of the survey tool.

Table 2. Perceived Impact of Variables on EDA (n = 135)

Patient Variable	Impact (%)			Addressed in Institutional Policy (%; n = 34)
	High to Very High	Moderate	None to Low	
Degree of obesity	69.7	17	13.3	80.8
CM*	67.9	23.7	8.4	53.8
PS	59.9	30.3	9.9	30.8
Age	48.1	32.3	19.6	26.9
Curative intent	78	16.7	5.3	50
Pharmacokinetic properties	49.6	34.6	15.8	26.9
Route of administration	18.8	37.6	43.6	23.1
Type of medication†	45.1	30.5	24.5	50

Abbreviations: EDA, empiric dose adjustment; CM, comorbidity; PS, performance status.

* Excluding renal or hepatic dysfunction.

† Targeted v cytotoxic chemotherapy.

Ambiguous and poorly worded questions were identified and reworked for the final survey. Pharmacists participating in the testing phase were not excluded from final survey distribution.

Survey Distribution

An introductory e-mail explaining the purpose of the survey also contained a link to SurveyMonkey (Menlo Park, CA), which collected all responses. Survey question design adhered to the methods established by Dillman.¹¹ However, because of the nature of e-mail distribution lists, only one mailing was possible. A survey link collected e-mail addresses of respondents who wished to receive survey results; the e-mail addresses were not linked to responses. We obtained an exempt review from the institutional review board of our institution.

Statistical Analysis

Descriptive statistics were used to evaluate the primary end point, common methods of EDA, and respondent demographics. Evaluation of the impact of a variable was performed using the Fisher's exact or χ^2 test where appropriate. Statistical tests were performed using Prism software version 5.02 (GraphPad, La Jolla, CA).

Results

Respondent demographics are listed in Table 1. Of the practitioners surveyed, 174 responded (response rate, 11%); 34 (19.7%) reported an institutional standard of practice regarding EDA of chemotherapy in obese adult patients. Degree of obesity, CM, curative intent, and type of medication were accounted for in most standards (Table 2). Specifics varied, with many using AdjBW40 to calculate BSA for patients who weighed more than 130% of their IBW. Use of IBW and capping of BSA mostly occurred in palliative therapy, with several practitioners using ABW in the adjuvant setting. There was no geographic trend in response.

When EDA was desired, the most common methods reported in our patient cases included using AdjBW40 to calculate BSA and capping BSA (Table 3). For carboplatin dosing, the most common method of EDA was calculating glomerular filtration rate (GFR);

Table 3. EDA Methods

Method	Overall Use (%)*
Based on BSA using IBW	10.5
Based on BSA using AdjBW25	16.6
Based on BSA using AdjBW40	36.3
Based on BSA using MBW	11.1
Reduce mg/m ² dosing but use ABW	3.2
Cap BSA	22.3

Abbreviations: BSA, body-surface area; IBW, ideal body weight; AdjBW25, adjusted body weight (ideal body weight + 25% of obese weight); AdjBW40, adjusted body weight (ideal body weight + 40% of obese weight); MBW, mean body weight; ABW, actual body weight.

* Percentage of all EDA responses, excluding carboplatin.

for the Calvert equation¹²) using AdjBW40 in the Cockcroft-Gault equation (C-G)¹³ (33.3%), followed by IBW in C-G (19.7%) and the Jelliffe equation¹⁴ (19.7%). The Salazar-Corcoran equation, an accurate predictor of GFR in obesity,¹⁵ was used in 1.8% of adjustments.

We assessed the perceived impact of patient characteristics on EDA. Most respondents considered degree of obesity, CM, PS, and curative intent to have the greatest impact on EDA (Table 2). As illustrated in Figure 1, curative intent, degree of obesity, PS, and age had significant impact on EDA in our patient cases. Type of medication (cytotoxic *v* targeted) was significant in the breast and colon cases ($P < .001$ and $P = .041$, respectively) but not in the lymphoma case (P was not significant for all scenarios). When comparing intravenous fluorouracil/leucovorin with oral capecitabine, there was no statistical difference ($P = .229$), indicating that route of administration does not affect EDA.

Discussion

It has been established that obesity is associated with increased cancer-related mortality, even when controlling for other variables.³ The reason for this is unclear, because cancer therapy is frequently multimodal and can include surgery, radiation therapy, and chemotherapy. There is concern that EDA of chemotherapy contributes to poorer outcomes in obese patients.

One fifth of respondents practiced at institutions with a standard for EDA of chemotherapy in obesity. Many standards included factors such as curative intent, age, and diagnosis. Our survey also showed that these variables affected the decision to perform EDA. Most policies used AdjBW40 to calculate BSA or capped the BSA at 2 m². Respondents did not specify whether this was because of the forced dose capping present in electronic health records, but awareness of their potential presence is important.

Overall, EDA was used in 46% of responses. In contrast, a survey of Australian oncologists found that more than 90% used EDA in chemotherapy for obesity.¹⁶ This may be a result of national differences in therapy and increasing evidence that EDA may not be necessary to minimize toxicity.^{17,18} An analysis of breast cancer adjuvant chemotherapy protocols from 1970 to 2000 also demonstrated this change over time.¹⁹ Before 1984, 95% of these trials permitted use of EDA for obesity; since 1984, that amount has decreased to 55%.

Our results show that the most common EDA methods were calculating BSA with AdjBW40 and capping BSA. IBW was used

Figure 1. Patient scenario results. ABW, actual body weight; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; BMI, body mass index; R, rituximab; PS, performance status; CM, comorbidity; AC, doxorubicin, cyclophosphamide; FOLFOX, leucovorin, fluorouracil, oxaliplatin; FU, fluorouracil; LCV, leucovorin.

less frequently. Field et al¹⁶ found that the most common methods of EDA for obesity were capping BSA or calculating BSA using IBW.

Degree of obesity, PS, and age affected EDA of chemotherapy for obesity, likely because of the impact on the risk-benefit ratio. However, multiple retrospective analyses observed that obese women treated for breast cancer using ABW did not have increased toxicity compared with normal women.^{17,19,20} Altering the number of CMs in our survey did not affect EDA.

We observed more EDA for treatment of metastatic disease, consistent with previous results showing that EDA is used less frequently in the adjuvant setting.¹⁶ Practitioners treat incurable patients with less intense doses to minimize toxicity, whereas dosing tends to be more aggressive in the adjuvant setting to maximize outcomes. An analysis of international breast cancer trials showed that obese women were more likely to receive a lower initial chemotherapy dose.¹⁷ This raises concern because estrogen receptor-negative obese patients who underwent EDA had worse overall and progression-free survival than obese patients who did not. In contrast, analyses of US colorectal trials suggest overall and progression-free survival in obese patients were not affected by EDA of adjuvant chemotherapy.^{21,22} This suggests that the effect of EDA on outcome varies with tumor type.

Trends in EDA are also related to type of therapy. Although we found that there was not a difference between intravenous and oral formulations of a fluoropyridine, there were some differences noted between use of cytotoxic and targeted agents. In targeted therapy, EDA was less frequent than in cytotoxic medications in cases 2 and 4, but there was no difference in EDA trends in case 3, potentially because of differences in dosing (mg/kg *v* mg/m²).

Carboplatin dosing was affected by degree of obesity. Dosed by estimating GFR to target a predefined area under the curve, carboplatin is one of the few chemotherapy agents not dosed on body size alone. More practitioners estimated GFR using ABW in the C-G, and dose-adjusted using AdjBW40 or IBW in the C-G, than used the Jelliffe method. Wright et al¹⁸ observed that using the Jelliffe method to estimate GFR in obese women caused less grade 3/4 toxicity but trended toward increased mortality. This may be why few practitioners in our survey used the Jelliffe method. The SCOTROC-1 (Scottish Randomised Trial in Ovarian Cancer) study used a measured GFR and exhibited no differences in mortality or toxicity between obese and normal-weight women, suggesting that use of estimates in obese patients is not optimal.²³

We noted differences between the perceived impact of a variable on EDA compared with case results. Although 78% of

respondents stated CM had a high impact on EDA, increasing the number of CMs in a patient case did not change results if PS was unchanged. Type of medication was considered a high-impact variable by 45.1% of respondents; however, it did not reach statistical significance in any of the cases. Although many factors affected EDA, they were not equally weighted.

Our survey results are limited by response rate. Because of the nature of the e-mail distribution lists used in our survey, repeat mailings were not conducted. The respondents who completed the demographics section were predominantly pharmacists practicing in academic medical centers. If the physician demographic is excluded, our response rate increases to 29%. It is unclear if the pharmacist-physician ratio was altered for the case responses.

Our results have helped to clarify current practice of EDA in obesity, which may help in the design of prospective trials. Although there is no standard of practice, the most frequently used EDA methods were using AdjBW40 in the BSA equation and capping BSA. Patients most likely to receive EDA were those of increased age, those who were more severely obese, and those who had worse PS. Additionally, type of medication and curative intent affected EDA. Identification of current practice will help in the development of prospective studies evaluating drug exposure, toxicity, and outcomes.

Accepted for publication on January 14, 2010.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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DOI: 10.1200/JOP.200016

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