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ORIGINAL PAPER

Toxicity and tolerability of adjuvant breast cancer chemotherapy in obese women

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Abstract The purpose of this study was to compare toxicity rates and types between obese and non-obese women during adjuvant chemotherapy for breast cancer, adjusting for regimen type and received dose. We conducted a retrospective cohort study of 537 women receiving chemotherapy, initially treated between 2007 and 2010 at two tertiary hospitals in Brisbane, Australia. Demographic, chemotherapy and toxicity data were extracted from patient charts and analyzed using multivariate logistic regression. Three hundred and seventy-four women were eligible for inclusion. Obese women (body mass index (BMI) > 30 kg/m^2; mean age 52.58 ± 9.49) were older than non-obese women (BMI ≤ 29.9 kg/m^2; mean age 50.19 ± 11.15, $P = 0.05$) and had more comorbidities ($P < 0.01$). After adjustment for potential confounders, obesity was not statistically related to chemotherapy-related admission risk (OR 1.27; 95 % CI 0.78–2.09) or febrile neutropenia risk (OR 0.56; 95 % CI 0.28–1.21). However, obese women received chemotherapy with proportionally lower mean relative dose intensity than non-obese women (94 vs. 97 % of reference dose, $P = 0.03$). Eighteen (15.8 %) obese and zero non-obese women ($P < 0.01$) had their chemotherapy dose capped at an arbitrary body surface area. Compared with non-obese women, obese women receive different chemotherapy regimens and relatively lower chemotherapy doses. There was no significant evidence of increased toxicity among obese women with either full or adjusted chemotherapy doses. Full body surface areas-based dosing appears to be tolerated as well in obese as in lean women.

Keywords Anti-neoplastic · Breast · Chemotherapy · Obesity · Toxicity

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Introduction

Optimizing chemotherapy dosage in obese women is a complex issue. Traditionally, obese women have received lower chemotherapy doses for their relative body size. These prophylactic dose reductions occurred following several pharmacokinetic studies suggesting higher exposure in obese women [1–4] to various chemotherapy agents (including 5-FU and doxorubicin), as well as isolated clinical trials reporting higher rates of toxicity [5]. More recently, however, evidence has emerged that dose reductions in obese women are associated with both reduced toxicity [6–8] and poorer outcomes [7, 9]. The majority of intentional dose reductions take the form of 'capping' the dose above certain body surface areas (BSA), commonly two m^2 [10], which correlates highly with body mass index (BMI). Dose capping may therefore contribute to the overall reduced survival seen generally in obese women with breast cancer [11].

Consequently, recent guidelines have suggested using full body surface area-based dosing [12]. These guidelines were based primarily on adjuvant therapy for non-breast malignancies (gynecological [13, 14] and colorectal [15, 16] predominating). Of the available breast cancer data, several studies reported on outdated chemotherapy regimens [10, 17] while others involved specific ethnic groups [8, 12] or clinical trial data [6, 7], which are not necessarily generalizable to real-world populations. Overall, there is relatively little evidence describing toxicity rates in obese women following implementation of full weight-based dosing. However, it would be expected that obese patients receiving full doses would experience similar toxicity rates to non-obese women. Overall, dose and tolerability and therefore efficacy should also be similar.

A retrospective cohort study was thus developed to quantify the relationship between body size, chemotherapy dose and toxicity at two tertiary centers in Queensland, Australia. Based on clinical concerns and the recent literature, we hypothesized that obese women would be relatively under-dosed for their actual body size, and further, would experience reduced toxicity levels compared with non-obese women.

Methods

To analyze chemotherapy dose and toxicity in breast cancer patients, a retrospective cohort study was devised. Ethical approval from the Hospital and University Research and Ethics Committees was attained (HREC/09; QPAH/313). Patients were identified through individual clinical pharmacy chemotherapy databases at each center. The medical charts were retrieved, and full demographic, chemotherapy, tumor and toxicity data were collected for analysis.

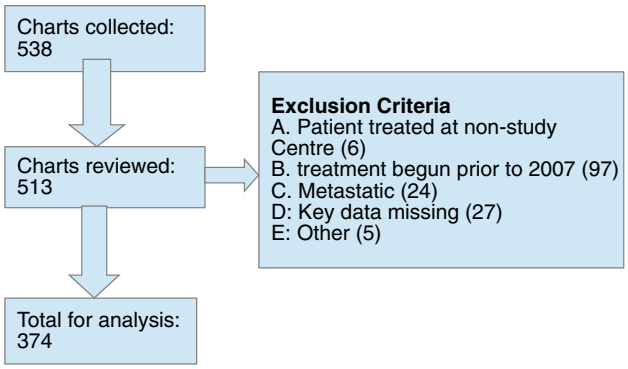

Fig. 1 Consort diagram

Participants

Women were eligible for inclusion if they were treated for non-metastatic (stage less than 4) breast cancer with adjuvant chemotherapy and had all chemotherapy courses through a single center. Exclusion criteria included women with metastatic disease; cancer other than breast; any chemotherapy cycles occurring outside the study centers, and lack of chemotherapy data. Key data including dose, weight, height, chemotherapy regimen and any regimen alterations, hospital admissions and adverse events were noted if they occurred (see Fig. 1). Eligibility was limited to treatment dates from 2007 and thereafter, due to changes in trastuzumab availability which influenced the choice and dose of chemotherapy combinations.

Chemotherapy regimens

Adjuvant chemotherapy was given as a combination, in three-weekly cycles. The predominant combination was 5-fluorouracil 500 mg/m^2, epirubicin 100 mg/m^2 and cyclophosphamide 500 mg/m^2 followed by docetaxel 100 mg/m^2 (FEC-T). Women with HER-2-positive tumors were usually treated with doxorubicin 60 mg/m^2/week and cyclophosphamide 600 mg/m^2/week, then docetaxel 100 mg/m^2 with trastuzumab at a 4 mg/kg loading dose and 2 mg/kg/week maintenance dose (ACTH). For these combinations, granulocyte colony-stimulating factor (G-CSF) was available prophylactically. Otherwise, a prior episode of severe neutropenia was required. Other regimens were used at the clinician's discretion where there was concern regarding toxicity or contraindications to particular agents. Body surface area was calculated using the Mosteller formula [18]. Women also received anti-estrogen therapy as indicated.

Variables

The main measure of dose was mean relative dose intensity (RDI), as described by Hryniuk et al. This is the ratio of actual chemotherapy dose in mg/m^2/week to the reference dose for that body surface area [19] and detects both delays and reductions in dose. Low RDI was defined as a mean RDI < 85 % of the reference dose, as described previously [20]. Key outcomes included occurrence of febrile neutropenia (FN; defined as absolute neutrophil count <1,000 cells per mm^3 + temperature > 38 °C) [21], which has been shown to correlate with chemotherapy efficacy [6, 22], and any hospital admissions during the chemotherapy treatment period.

Data were stratified by BMI into obese (≥30 kg/m^2) and non-obese (<30 kg/m^2) based on weight and height at the time of the first chemotherapy cycle.

Statistical analysis

Univariate statistics were performed using chi-square tests for categorical variables and Student's *T* test for normally distributed continuous variables. Nonparametric variables were compared using the Mann–Whitney *U* test. Multivariate analyses were performed using logistic regression, adjusting for age, stage and grade of tumor at diagnosis, number of comorbidities, smoking status, treating hospital, receipt of other adjuvant treatment or G-CSF, and type of chemotherapy. Two-sided probability testing was used for all probability testing. All calculations were performed using SPSS Statistics 20 (IBM Corp., Armonk, NY).

Results

Of 537 women assessed, 374 met the inclusion criteria (Fig. 1). Of these, 30.5 % were obese, with a mean BMI for the cohort of 27.7 kg/m^2. A variety of chemotherapy regimens were used—the most common being FEC-T (158 women, 42.3 %); docetaxel/cyclophosphamide (TC; 58 women, 15.6 %); docetaxel/doxorubicin/cyclophosphamide (TAC; 40 women, 10.7 %) and TCH (docetaxel/carboplatin; 38 women, 10.2 %). Prophylactic G-CSF was used in 111 women (29.7 %). An institutional effect was noted—32 (87 %) of women treated with TCH, and 31 (100 %) treated with FEC were from a single institution. Interestingly, prophylactic G-CSF was not used in 67 women (91.6 %) from one institution, despite its availability. Mean RDI of the cohort was 96 % of the reference dose. A mean RDI < 85 % of the reference occurred in 61 women (16.3 %).

Effect of obesity

Obese women (mean age 52.58 years, SD 9.49) were older than non-obese women (mean age 50.19 years, SD 11.15; $P = 0.05$) and demonstrated a greater frequency of comorbid disease (mean 1.79 comorbidities vs. mean 1.08 comorbidities in non-obese women; $P < 0.001$) (Table 1). Regimens that have been demonstrated to be higher toxicity in previous studies (FECT, ACTH, ACP, TAC) [23] occurred less frequently among obese women (OR 0.82, 95 % CI 0.68–0.99).

Obese women received overall lower chemotherapy doses for their BSA. This was seen in both first-cycle dose reductions (proportion of reference dose 98 vs. 99 %; $P < 0.01$) and overall lower dose intensities (mean RDI 0.94 vs. 0.97; $P = 0.02$) (Table 1). Eighteen instances of deliberate dose capping were identified (15.6 %; 14 at BSA 2.0 m^2, two at 2.1 m^2 and two at 2.2 m^2). All were obese (mean BMI 38.8 kg/m^2). Despite this, in the multivariate analysis, obesity did not influence the risk of low RDI (<85 %; OR 1.08, 95 % CI 0.56–2.06) (Table 2). Post hoc analysis after exclusion of dose-capped patients demonstrated no significant difference in mean RDI between obese and non-obese patients (RDI 0.95 vs. 0.97, $P = 0.21$).

Admissions to hospital occurred in 47.6 % of obese women compared with 35.9 % of non-obese women, a non-significant difference. In multivariate analysis, obesity was not related to admission risk (OR 1.27; 95 % CI 0.78–2.09). Obese patients appeared almost half as likely to develop FN compared with non-obese women (OR 0.56; 95 % CI 0.28–1.21), although this did not quite reach significance ($P = 0.09$) (Table 2). These results were similar after exclusion of dose-capped obese patients (admission OR 1.29, 95 % CI 0.79–2.12; FN OR 0.68, 95 % CI 0.32–1.42).

Dose

Dose intensity was generally well maintained (mean 0.96). Low dose (mean RDI < 85 % of the reference) occurred in 61 women (16.3 %). Multivariate analysis, including age, chemotherapy types and CSF prophylaxis did not identify any significant predictors (Table 2).

Toxicity

One hundred and fifty-five (41.4 %) patients were admitted to hospital during their chemotherapy regimen. The main predictor of hospital admission rates was higher comorbidity scores (OR 1.22, 95 % CI 1.04–1.43 per additional comorbidity) (Table 2). Admission rates were not influenced by type of chemotherapy regimen, age, dose capping or use of CSF prophylaxis. Reason for admission is described in Table 3. No significant differences between obese and non-obese women were observed.

Overall, 53 (14.2 %) patients developed FN. The only significant predictor for FN was use of taxane-based

Table 1 Characteristics of obese and non-obese patients

Variable	BMI ≤ 30 (%) ($N = 260$)	BMI > 30 (%) ($N = 114$)	P value
Mean age ± SD	50.19 ± 11.2	52.58 ± 9.5	0.05
Mean BMI ± SD	24.46 ± 3.1	35.1 ± 4.5	<0.001
Mean BSA ± SD	1.72 ± 0.2	2.02 ± 0.2	<0.001
Smoker (ever)	111 (42.7)	52 (45.6)	0.63
Type of cancer			
Ductal	205 (79.5)	92 (80.7)	0.61
Lobular	33 (12.8)	17 (14.9)	
Mixed	19 (7.4)	5 (4.4)	
Grade			
1	15 (5.8)	5 (4.4)	0.68
2	105 (40.5)	51 (44.7)	
3	140 (58.3)	58 (50.9)	
Stage			
1	52 (20.2)	23 (20.2)	0.70
2	141 (54.9)	67 (58.8)	
3	64 (24.9)	24 (21.1)	
ER positive	188 (72.3)	87 (73.7)	0.91
PR positive	171 (69.8)	77 (71.3)	0.78
HER-2-positive	50 (20.5)	22 (20.4)	0.70
Chemotherapy regimen			
FECT	110 (42.5)	48 (42.1)	0.15
ACTH	14 (5.4)	4 (3.5)	
ACT	34 (13.1)	6 (5.3)	
Non-taxane			
FEC	19 (7.3)	12 (10.5)	
AC	10 (3.9)	3 (2.6)	
Non-anthracycline			
TC	37 (14.3)	21 (18.4)	
TCH	21 (8.1)	16 (14.0)	
Breast-conserving surgery	117 (50.0)	55 (48.3)	0.33
Radiotherapy	214 (82.3)	99 (86.8)	0.52
Dose capping	0 (0)	18 (15.8)	<0.001
Hormonal therapy			
Tamoxifen	90 (34.9)	32 (28.3)	0.55
Aromatase inhibitor	89 (34.5)	45 (39.8)	
Goserelin	10 (3.9)	4 (3.5)	
Treatment hospital A	84 (32.3)	40 (35.1)	0.63
CSF prophylaxis	78 (30.2)	33 (28.9)	0.30
Mean no. comorbidities ± SD	1.08 ± 1.31	1.79 ± 1.7	0.02
Mean FCDP ± SD	0.99 ± 0.06	0.98 ± 0.04	<0.001
Mean RDI ± SD	0.97 ± 0.16	0.94 ± 0.3	0.02
Admission	103 (39.6)	52 (45.6)	0.30
Febrile neutropenia	42 (16.2)	11 (9.2)	0.09

FECT: 5-fluorouracil, epirubicin, cyclophosphamide, docetaxel; ACTH: doxorubicin, cyclophosphamide, docetaxel, herceptin; TC: docetaxel and cyclophosphamide; TCH: docetaxel, carboplatin, herceptin; FCDP: first-cycle dose proportion; RDI: relative dose intensity

regimens (TC, TCH; OR 2.3; 95 % CI 1.04–5.11). No patients who were dose-capped developed FN, although there were only 18 cases.

Discussion

In this cohort of Australian women with breast cancer, obese women experienced altered adjuvant chemotherapy treatment compared with lean women, perhaps due to concerns regarding toxicity if full doses were given. Specifically, we observed altered chemotherapy regimen type, with a reduced frequency of high-toxicity regimens, as well as deliberate capping of BSA in dose calculations in the obese group.

Such regimen changes did not occur secondary to increased toxicity. In fact, dose-related toxicity, measured by FN [6, 22], was observed almost half as frequently in obese women (OR 0.56; 95 % CI 0.28–1.21; $P = 0.09$). With a larger sample size, these results would likely have reached statistical significance. This reduction in dose-related toxicity was observed despite a greater proportion of obese patients allocated to chemotherapy regimens that were also significant contributors to FN risk (TCH, TC). There may be some form of compensating or neutropenia-protective mechanism operating in obese women—for example, increased chemotherapy clearance due to up-regulation of cytochrome P450 genes secondary to dietary factors [24]. Alternatively, it may simply reflect the relatively lower overall chemotherapy doses received by obese women. However, this possibility is less likely given that non-capped obese patients, accounting for 85 % of the cohort, achieved equivalent dose intensities to non-obese women, and showed similar reductions in FN rate. These data confirm that obese women tolerate full dosing as well as lean women.

There was also no significant difference between obese and non-obese women in hospital admission rates, although both groups were admitted more frequently than clinical trials would suggest [25, 26]. Although a greater proportion of obese women were admitted to hospital, this was likely due to confounding from greater comorbid disease burden among obese women, which remained a predictor in multivariate analysis. The presence of comorbidities may thus be the real driver of admission, rather than obesity. The increased hospitalization rate may be the result of exacerbation of comorbidities by chemotherapy (including cardiovascular disease with anthracyclines and trastuzumab) [27–29]; or reduced physiological reserve in women with multiple comorbidities; or simply be due to a lower threshold for admission in these complicated patients. Indeed, we posit that the generally higher admission rates seen in this group demonstrates the difference between

Table 2 Multivariate analyses of outcomes in adjuvant breast cancer chemotherapy

Variable	Febrile neutropenia OR (95 % CI)	Hospital Admission OR (95 % CI)	RDI < 85 % OR (95 % CI)
Age			
<46	1.00	1.00	1.00
46–56	0.98 (0.47–2.05)	1.20 (0.71–2.05)	1.46 (0.68–3.00)
>56	0.74 (0.32–1.67)	0.99 (0.56–1.77)	1.65 (0.76–3.58)
Chemotherapy regimen[a]			
Taxane/anthracycline-based	1.00	1.00	1.00
Non-taxane-based	0.78 (0.24–2.58)	0.70 (0.33–1.48)	1.60 (0.65–3.96)
Non-anthracycline-based	2.30 (1.04–5.11)	1.16 (0.64–2.09)	1.45 (0.69–3.05)
Relative dose intensity			
≥85 %	1.00	1.00	–
<85 %	0.8 (0.33–1.90)	1.63 (0.90–2.94)	
Smoking status			
Non-smoker	1.00	1.00	1.00
Smoker	1.70 (0.91–3.15)	0.92 (0.60–1.43)	0.82 (0.46–1.47)
Comorbidity score			
Per additional comorbidity	0.98 (0.78–1.24)	1.22 (1.04–1.43)	1.05 (0.86–1.28)
Body mass index (BMI)			
<30	1.00	1.00	1.00
Obese (>30)	0.63 (0.30–1.29)	1.27 (0.78–2.09)	1.08 (0.56–2.06)
CSF prophylaxis			
No	1.00	1.00	1.00
Yes	1.57 (0.62–3.98)	1.00 (0.59–1.69)	0.68 (0.32–1.43)
Stage			
Stage 1	1.00	1.00	1.00
Per additional stage	1.54 (0.94–2.52)	1.09 (0.77–1.56)	1.05 (0.65–1.67)
Dose capped[b]			
No	–	1.00	1.00
Yes		0.40 (0.13–1.21)	1.24 (0.35–4.42)

[a] Non-taxane chemotherapy (FEC, AC) and non-anthracycline chemotherapy (TC, TCH) relative to anthracycline/taxane chemotherapy (FEC-T, ACTH, TAC)

[b] There were no dose-capped individuals who developed FN

real-world and clinical trial management of adverse effects during chemotherapy. In the real world, these patients are treated very carefully and often admitted briefly for fear of complications. It is likely that all of these patients, but particularly those with high comorbid disease rates, could benefit from more intense follow up and enhanced liaison with community doctors, reducing unnecessary admission rates.

The other key predictor of chemotherapy-related toxicity was the chemotherapy regimen. However, the anticipated high-toxicity regimes, particularly FEC-T, did not develop the expected relatively high toxicity rates. Instead, TCH and TC, typically used in Australia as low-toxicity regimens [23], recorded the highest rate of FN. These taxane-containing alternatives to anthracycline-based chemotherapy are relatively new regimens. In Australia, they are not currently eligible for primary G-CSF prophylaxis, due to the limited evidence base for both efficacy and toxicity [23]. One large trial of TC showed efficacy equivalent to FEC-T, with lower rates of toxicity [30]. TCH has been described in a number of phase II trials, but lacks large-scale efficacy or toxicity data. Moreover, no study has specifically examined the effect of obesity on outcomes for these newer combinations. It may be that altered regimen choice in obese women has contributed to the poorer survival among these women.

Several limitations to this study were identified. First, this was a retrospective study. The data are thus limited to what was routinely recorded in the hospital charts. Some toxicity, such as FN, is defined by specific criteria, and failure to record some of these figures prevents a diagnosis of FN. In addition, toxicities and admission may have been missed due to presentations to other hospitals. Obese women, with generally lower socioeconomic status, are less likely to have access to transport, which may lead to presentation elsewhere. Another potential factor affecting the results is the relatively small sample size, which was limited by the size of the available database. However, this did have the advantage in allowing more complete data to be extracted relating to toxicities and admission details.

Table 3 Reason for hospital admission by obesity status

Reason for admission	Total (%) ($N = 152$)	BMI < 30 (%) ($N = 103$)	BMI ≥ 30 (%) ($N = 49$)
Cardiac	3 (2.0)	1 (1.0)	2 (4.1)
Vascular	7 (4.6)	4 (3.9)	3 (6.1)
VTE	5 (3.3)		
Non-neutropenic fever	36 (23.7)	24 (23.3)	12 (24.5)
Other infection	22 (14.5)	12 (11.7)	10 (20.4)
Urinary	2 (1.3)		
Respiratory	5 (3.3)		
Cellulitis	5 (3.3)		
Febrile neutropenia	57 (37.5)	44 (42.7)	13 (26.5)
Gastrointestinal	15 (9.9)	12 (11.7)	3 (6.1)
N &V	7 (4.6)		
Diarrhea	5 (3.3)		
Neurological	2 (1.3)	2 (1.9)	0 (0.0)
Stroke	1 (0.7)		
Planned or social	2 (1.3)	2 (1.9)	0 (0.0)
Renal	3 (2.0)	1 (1.0)	2 (4.1)
ARF	2 (1.3)		
Dermatological	2 (1.3)	1 (1.0)	1 (2.0)
Rash	2 (1.3)		
Other	3 (2.0)	0 (0.0)	3 (6.1)

VTE venous thromboembolism; *N & V* nausea and vomiting; *ARF* acute renal failure

Further, in order to increase the size of the data set from these hospitals, data prior to 2007 must be used, with the consequence of significant alterations to available chemotherapy regimens (trastuzumab was not available).

Conclusion

In this cohort of Australian women with non-metastatic breast cancer, obese women received slightly lower doses of chemotherapy for their body size as well as different chemotherapy regimens than non-obese women. While no significant differences in toxicity were seen, there was a roughly 50 % reduction in FN rate in obese women. Importantly, no increase in toxicity rates was seen in non-capped obese women. This suggests obese women tolerate full dosing. Further research including pharmacokinetic and outcome data in obese women who are not dose-capped is needed to answer this question and provides evidence-based guidance for dosing chemotherapy in obese women with breast cancer.

Conflict of interest None.

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