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Obesity is not associated with increased myelosuppression in patients receiving chemotherapy for breast cancer

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ABSTRACT

Audits of adjuvant chemotherapy for breast cancer have revealed that obese patients receive a lower relative dose intensity (RDI). However, interpretation of these studies is complicated by the variable use of cytokine growth factors, empiric dose capping and first cycle dose reductions. We have analysed the impact of obesity on RDI in a cohort of 662 patients that is not confounded by these factors. Patients were classified as overweight or obese on the basis of a body mass index (BMI) $\geqslant 25\ kg/m^2$. The mean RDI in patients with BMI $\geqslant 25\ kg/m^2$ was actually significantly greater than in those with BMI $<25\ kg/m^2$ ($p = 0.03$). Overweight patients were less likely to experience cycle delays due to prolonged myelosuppression ($p < 0.001$), particularly towards the end of the treatment course. We conclude that drug doses need not be reduced on the basis of obesity. Overall obese patients are in fact less likely to suffer haematological toxicity.

1. Introduction

Obesity is associated with an increased risk of developing breast cancer after the menopause.[1] In addition obese women with breast cancer have a worse prognosis than their lean counterparts, even after controlling for known prognostic factors.[2,3] The mechanism for this association remains uncertain but it seems likely that in post-menopausal women higher circulating oestrogen levels, as a consequence of increased aromatase activity in excess body fat, alters the course of the disease. Another factor that may be relevant to the poorer outcomes seen in this group of patients is the inadequate doses of adjuvant chemotherapy delivered.[4] There is a tendency for clinicians to institute empiric dose reductions in overweight patients, motivated by concerns that dosing in relation to actual body weight puts them at higher risk of toxicity. These reductions can take the form of capping the body surface area (BSA) at $2\ m^2$, first cycle dose reductions and the use of the ideal rather than actual body weight to calculate BSA. Recent audits have revealed how frequent this practice is.[5,6] However, despite the widespread nature of these dose modifications, evidence that obese women are genuinely at increased risk of myelosuppression remains scanty. Given the prevalence of obesity in western societies, the optimal dosing regime for overweight patients will become increasingly important for medical oncologists.

To investigate the impact of body size on myelosuppression and received dose intensity, we examined a cohort of patients that is not confounded by *a priori* dose reductions or the use of granulocyte colony stimulating factor. As far as we are aware, no previous study has attempted to assess the effect of obesity on haematological toxicity alone over the entire course of adjuvant chemotherapy.

2. Patients and methods

Using our patient management information system, an electronic database through which chemotherapy is prescribed,

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we identified all patients treated with FEC chemotherapy for breast cancer. The regimen employed (5-fluorouracil 600 mg/m^2, epirubicin 60 mg/m^2, cyclophosphamide 600 mg/m^2 administered intravenously every 3 weeks) has been reported previously.[7] Over a 4 year period (January 2001–December 2004), a total of 662 patients received neo-adjuvant or adjuvant FEC. Patients were planned to receive a minimum of six cycles of treatment. Chemotherapy was dosed for all patients on the basis of BSA, computed using the formula (height$^{0.725}$ × weight$^{0.425}$ × 0.20247).[8] Neither *a priori* dose reductions nor BSA capping were employed for any of the patients. A dose-banding algorithm was used to facilitate the reconstitution of drugs in our cytotoxic pharmacy. The actual doses prescribed were within ±5% of the calculated doses based on BSA.

Throughout the period of this audit, an institutional policy for the prescription of chemotherapy was in operation. Each cycle of treatment was delivered if the absolute neutrophil count on the planned day of delivery was ⩾1.5 and the platelet count ⩾100. If not chemotherapy was delayed for 1 week. If chemotherapy was delayed on more than one occasion, a dose reduction of 20% was made for all agents and maintained for the rest of the treatment course. Greater dose reductions were instituted if the patient experienced further myelosuppression despite these modifications. The Gloucestershire Oncology Centre operates a 24 h telephone helpline and dedicated neutropaenic ward for the admission of all patients with febrile neutropaenia. After an episode of neutropaenic sepsis, doses were also reduced by 20%. Cytokine growth factors were not employed as either primary or secondary prophylaxis after neutropaenic events. No patient received concomitant radiotherapy and endocrine treatment was only commenced after completion of chemotherapy.

The actual doses delivered, timing of each cycle and occurrence of febrile neutropaenia were obtained for each patient by searching the electronic database. In cases, where there was a dose reduction or cycle delay, the oncology records were reviewed to determine the cause for the alteration in treatment schedule.

We have classified women as obese on the basis of BSA ⩾2 m^2, a common cut-point at which dose capping is undertaken. A second measure of obesity that is widely used in epidemiological studies is the body mass index (BMI) defined as the weight (kg) divided by the squared height (m). BMI categories are defined by the World Health Organisation.[9] Individuals with a BMI ⩾25 kg/m^2 are considered overweight or obese.

Relative dose intensity (RDI) was defined as (dose received/dose planned)/(overall treatment time/projected treatment time) over six cycles of treatment.[10] This was considered to be sub-optimal if it fell below 85%.[11]

Group comparisons for continuous variables were performed using Student's *t*-test. χ^2-tests were used to determine the significance of differences between categorical variables. All tests for significance were two-tailed. SPSS software was used for the statistical analyses.

3. Results

As would be expected for a population receiving adjuvant chemotherapy, the majority of patients in this study had high grade tumours and involved locoregional lymph nodes. Patient and tumour characteristics are given in Table 1. The population distribution for BSA and BMI is shown in Fig. 1. As defined by BMI ⩾25, 366 (55%) of the population would be classified as overweight or obese. In contrast, only 77 (12%) would have been identified as large using a BSA ⩾2 m^2. Of note is the observation that 73 out of the 77 patients (95%) with a BSA ⩾2 m^2 were overweight or obese by the World Health Organisation definition. Furthermore, the correlation coefficient between BMI and BSA was strong (r = 0.75). Thus, in this cohort of breast cancer patients, high BSA is primarily a consequence of obesity.

The mean RDI administered for the entire cohort was 92.6%. Two hundred and ninety-five patients (45%) suffered unplanned schedule interruptions or dose reductions. The cause for the reduction in RDI in these patients was categorised as haematological toxicity 170 (26%), non-haematological toxicity 55 (8%), social (public holidays, prior engagements) 15 (2%), unrelated medical conditions 15 (2%), progressive disease 7 (1%), patient request 7 (1%) or a combination of these 27 (4%).

To investigate the impact of obesity on haematological toxicity alone, we excluded the 126 patients with other causes for dose modifications or delays from the subsequent analysis. For the remaining 536 patients, the mean RDI was 95.0% and 86 patients received less than 85% of the planned RDI due to myelosuppression. No difference was seen in mean RDI between patients with a BSA <2 m^2 (94.9%) and those with BSA ⩾2 m^2 (95.8%) (p = 0.48). BMI was also used to define obesity. This variable was divided into two groups: normal/

Table 1 – Patient characteristics

Mean age	49.8 (range 22–69)
>50	357
>65	18
Node positive	371 (56%)
Node negative	249 (38%)
Node unknown	42 (6%)
Grade 1	35 (5%)
Grade 2	201 (30%)
Grade 3	388 (59%)
Grade unknown	38 (6%)
ER positive	450 (68%)
ER negative	204 (31%)
ER unknown	8 (1%)
Neo-adjuvant/adjuvant	34/628
Mean BSA (m^2)	1.75 (range 1.4–2.3)
BSA ⩾2 m^2	77 (12%)
Mean BMI (kg/m^2)	26.27 (range 17.9–49.6)
Underweight (<18.5)	6 (1%)
Normal weight (18.5–24.9)	290 (44%)
Overweight (25–29.9)	248 (37%)
Obese (30–39.9)	108 (16%)
Morbidly obese (40+)	10 (2%)

Abbreviations: BSA, body surface area; BMI, body mass index. Node status and tumour grade were classed as unknown for patients receiving neo-adjuvant chemotherapy.

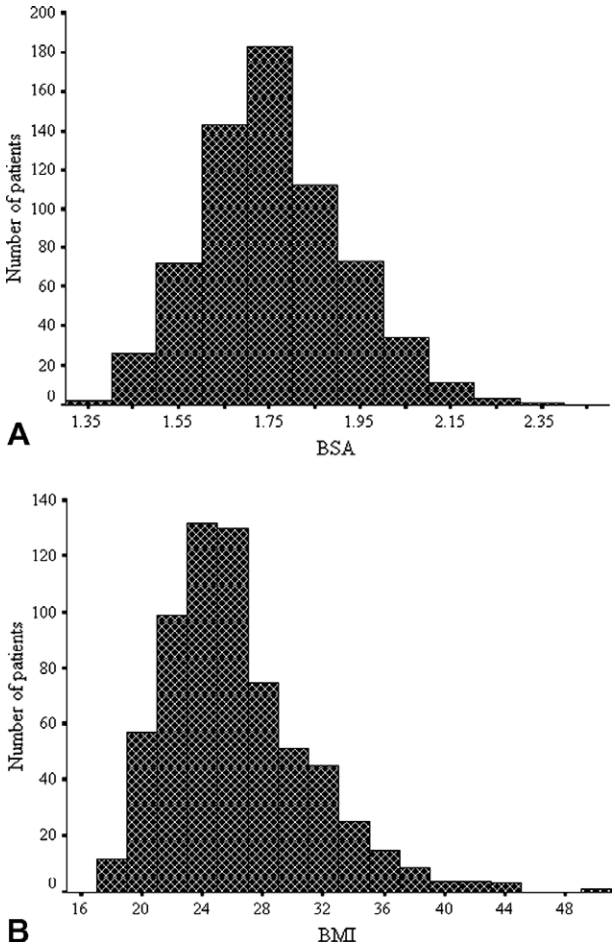

Fig. 1 – Population distribution for body surface area (BSA, panel A) and body mass index (BMI, panel B).

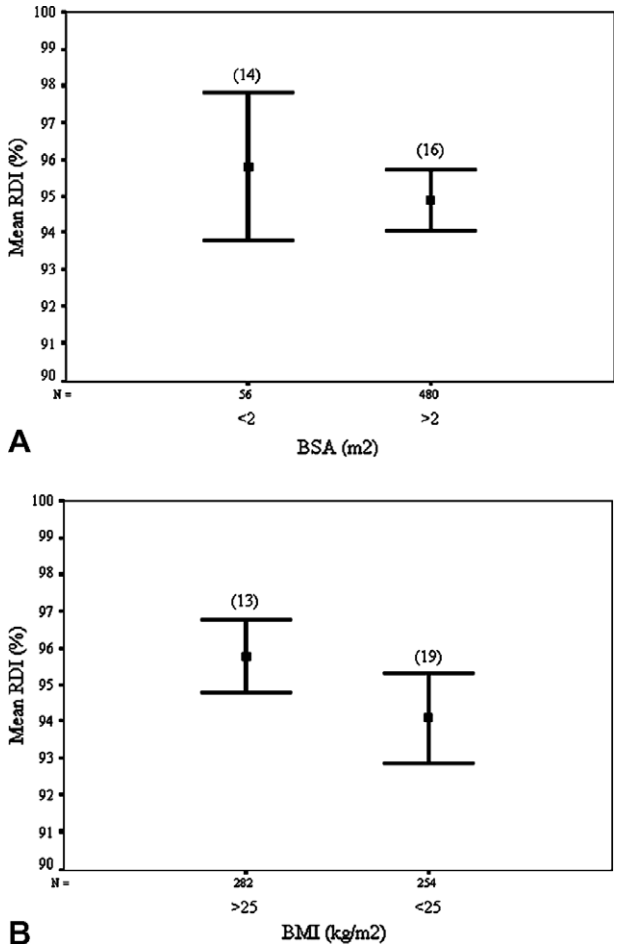

Fig. 2 – Relative dose intensity (mean and standard error) for patients defined by a body surface area of ⩾2 m^2 (panel A) or body mass index of ⩾25 kg/m^2 (panel B). The mean RDI in patients with a BMI of ⩾25 kg/m^2 was significantly higher than patients with a BMI < 25 kg/m^2 ($p = 0.03$). Figures in parentheses represent the percentage of patients in each group that failed to achieve an RDI of ⩾85% of that intended.

underweight and overweight/obese using a cut-point of 25 kg/m^2. The mean administered dose intensity in the overweight/obese patients was 95.8%, compared with 94.1% in non-obese patients ($p = 0.03$) (Fig. 2).

We were interested in determining the origin of the higher RDI seen in overweight patients. Using our institutional prescribing policy described earlier, the dose intensity of chemotherapy could be reduced as a consequence of neutropaenic sepsis or failure of marrow recovery by the time of the next planned course of treatment. The relative contributions of these two mechanisms to the difference in RDI seen in the two BMI categories were investigated. Overall 139 patients had ⩾1 week prolongation in their chemotherapy course. The number of patients experiencing such a delay was significantly lower in patients with a BMI ⩾25 compared with patients with a BMI <25 (55/282 (20%) *versus* 84/254 (33%), $p < 0.001$). Neutropaenic fever was rare. Only 45 patients experienced one or more episodes of neutropaenic fever. However, paradoxically this complication was somewhat more common in overweight patients (31/282 (11%) *versus* 14/254 (6%), $p = 0.02$).

Finally, to determine whether the temporal pattern of neutropaenic events was different in obese and non-obese groups, we studied their frequency in each cycle of chemotherapy (Fig. 3). In the obese treatment, delays due to myelosuppression become less common toward the end of the course of chemotherapy. Furthermore, the difference in the number of treatment delays between the two groups becomes increasingly more pronounced after the third cycle of FEC. In contrast, 42% of all the episodes of neutropaenic fever follow the first cycle of treatment (Fig. 3).

4. Discussion

BSA based dosing has been widely adopted in oncology as a means of safely administering cytotoxic drugs. However, even after normalising drug dose to body size, there is a wide variability in pharmacokinetics for most agents which reflects inter-patient variability in drug metabolism and elimination.[12] For several drugs there is little correlation between BSA and clearance. In the light of this, many clinicians are wary of scaling up doses for obese patients thereby exposing them to greater risks of toxicity. As a result, several dose-cap-

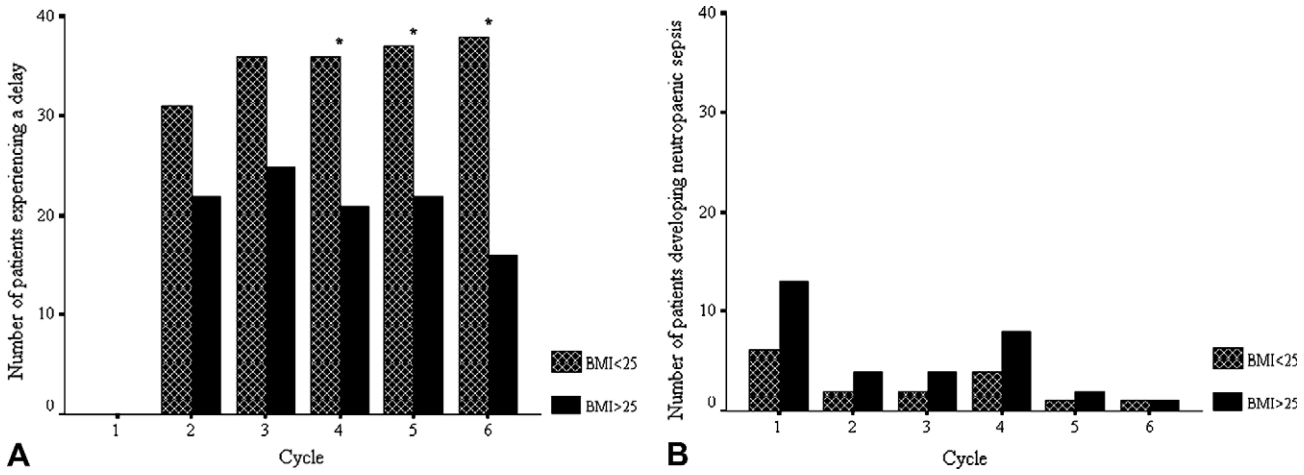

Fig. 3 – Chemotherapy delays (panel A) and episodes of neutropaenic fever (panel B) displayed for successive cycles of chemotherapy for patients categorised on the basis of a body mass index <25 kg/m^2 or ⩾25 kg/m^2. Asterisks mark statistically significant differences ($p < 0.05$) between the two groups.

ping strategies have been employed to limit the actual doses received in this group of patients. A large study of breast cancer chemotherapy practice confirmed that overweight patients are more likely to receive lower doses.[13] This arose almost entirely due to a higher frequency of planned dose reductions at the time of initial treatment. There was little difference in the need for unplanned dose modifications owing to toxicity.[13] Such sub-optimal dose intensity may partly explain the adverse clinical outcome in these patients, since failure to deliver a minimal threshold of dose intensity appears to compromise the efficacy of adjuvant chemotherapy.[14]

Our findings are consistent with previous audits of chemotherapy practice.[13] Unplanned dose reductions due to myelosuppression are surprisingly common, occurring in 26% of patients treated. Moreover, 13% of patients failed to achieve 85% of their RDI as a result of haematological toxicity and 7% had an episode of neutropaenic fever. These figures are lower than those previously reported, perhaps reflecting the doses of the FEC regimen that we employed and the more rigorous exclusion of non-neutropaenic causes of reduced dose intensity. Importantly we found no evidence to indicate that overall myelosuppression was more common in obese patients when dosed according to actual body weight. This finding is in keeping with the results of two previous studies that have looked at the impact of obesity on haematological toxicity after the first cycle of chemotherapy. In patients who receive weight based dosing, Rosner and colleagues found that there was no relationship between obesity and grade 3 haematological toxicity.[4] Poikonen and colleagues found that obese patients actually have higher leucocyte nadirs than non-obese counterparts.[15] There are several possible explanations for the reduced myelosuppression in obese patients. Overweight women have higher levels of obesity associated protein leptin, which has been shown to stimulate haemopoiesis.[16,17] Alternatively excess body fat may alter the pharmacokinetics of cytotoxic drugs although paradoxically, where this has been studied, obesity correlates with reduced clearance and increased drug exposure.[18,19]

In the present study, interesting differences were seen between the obese and non-obese populations in both the type of neutropaenic event and their frequencies during the course of chemotherapy. Most notably patients with higher BMI were significantly less likely to suffer treatment delays. One possible interpretation of these data is that on the whole obese patients are more resistant to moderate degrees of chemotherapy induced myelosuppression which usually results in deferment of the next cycle. This protective effect is more evident towards the end of treatment course, suggesting that the mechanism is acquired. However, there also exists a subset of breast cancer patients prone to develop severe marrow suppression and neutropaenic sepsis. This is more prevalent after the first cycle of treatment implying *de novo* susceptibility. Neutropaenic sepsis is more common in obese patients with this susceptibility phenotype due to the higher absolute doses received by this group.

In conclusion, we have confirmed that overweight breast cancer patients receiving adjuvant chemotherapy are not at excessive risk of myelosuppression if dosed according to their actual body weight. Similar findings have been reported for adjuvant therapy in colon cancer.[20] Indeed in some regards individuals with a higher BMI appear to tolerate chemotherapy better than their non-obese counterparts. Breast cancer patients should therefore receive doses of chemotherapy calculated on the basis of their actual BSA, regardless of size.

Conflict of interest statement

None.

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REFERENCES

1. van den Brandt PA, Spiegelman D, Yaun SS, et al. Pooled analysis of prospective cohort studies on height, weight, and breast cancer risk. *Am J Epidemiol* 2000;**152**:514–27.
2. Bastarrachea J, Hortobagyi GN, Smith TL, Kau SW, Buzdar AU. Obesity as an adverse prognostic factor for patients receiving adjuvant chemotherapy for breast cancer. *Ann Intern Med* 1994;**120**:18–25.
3. Berclaz G, Li S, Price KN, et al. Body mass index as a prognostic feature in operable breast cancer: the International Breast Cancer Study Group experience. *Ann Oncol* 2004;**15**:875–84.
4. Rosner GL, Hargis JB, Hollis DR, et al. Relationship between toxicity and obesity in women receiving adjuvant chemotherapy for breast cancer: results from cancer and leukemia group B study 8541. *J Clin Oncol* 1996;**14**:3000–8.
5. Madarnas Y, Sawka CA, Franssen E, Bjarnason GA. Are medical oncologists biased in their treatment of the large woman with breast cancer? *Breast Cancer Res Treat* 2001;**66**:123–33.
6. Griggs JJ, Sorbero ME, Lyman GH. Undertreatment of obese women receiving breast cancer chemotherapy. *Arch Intern Med* 2005;**165**:1267–73.
7. Mouridsen H, Andersen J, Andersson M, Dombernowsky P. Adjuvant anthracycline in breast cancer. Improved outcome in premenopausal patients following substitution of methotrexate in the CMF combination with epirubicin. *Proc Am Soc Clin Oncol* 1999;**19**:68a [abstr 254].
8. DuBois D, DuBois E. A formula to estimate the approximate surface area if height and weight be known. *Arch Intern Med* 1916;**17**:863–71.
9. Report 854. Physical status: the use of interpretation of anthropometry: report of a WHO expert committee; 1995. p. 1–452.
10. Longo DL, Duffey PL, DeVita Jr VT, Wesley MN, Hubbard SM, Young RC. The calculation of actual or received dose intensity: a comparison of published methods. *J Clin Oncol* 1991;**9**:2042–51.
11. Bonadonna G, Valagussa P, Moliterni A, Zambetti M, Brambilla C. Adjuvant cyclophosphamide, methotrexate, and fluorouracil in node-positive breast cancer: the results of 20 years of follow-up. *New Engl J Med* 1995;**332**:901–6.
12. Gurney H. Dose calculation of anticancer drugs: a review of the current practice and introduction of an alternative. *J Clin Oncol* 1996;**14**:2590–611.
13. Lyman GH, Dale DC, Crawford J. Incidence and predictors of low dose-intensity in adjuvant breast cancer chemotherapy: a nationwide study of community practices. *J Clin Oncol* 2003;**21**:4524–31.
14. Budman DR, Berry DA, Cirrincione CT, et al. Dose and dose intensity as determinants of outcome in the adjuvant treatment of breast cancer. The Cancer and Leukemia Group B. *J Natl Cancer Inst* 1998;**90**:1205–11.
15. Poikonen P, Blomqvist C, Joensuu H. Effect of obesity on the leukocyte nadir in women treated with adjuvant cyclophosphamide, methotrexate, and fluorouracil dosed according to body surface area. *Acta Oncol* 2001;**40**:67–71.
16. Gainsford T, Alexander WS. A role for leptin in hemopoieses? *Mol Biotechnol* 1999;**11**:149–58.
17. Wilson CA, Bekele G, Nicolson M, Ravussin E, Pratley RE. Relationship of the white blood cell count to body fat: role of leptin. *Br J Haematol* 1997;**99**:447–51.
18. Powis G, Reece P, Ahmann DL, Ingle JN. Effect of body weight on the pharmacokinetics of cyclophosphamide in breast cancer patients. *Cancer Chemother Pharmacol* 1987;**20**:219–22.
19. Rodvold KA, Rushing DA, Tewksbury DA. Doxorubicin clearance in the obese. *J Clin Oncol* 1988;**6**:1321–7.
20. Meyerhardt JA, Catalano PJ, Haller DG, et al. Influence of body mass index on outcomes and treatment-related toxicity in patients with colon carcinoma. *Cancer* 2003;**98**:484–95.