Effect of Obesity on the Leukocyte Nadir in Women Treated with Adjuvant Cyclophosphamide, Methotrexate, and Fluorouracil Dosed According to Body Surface Area

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Acta Oncologica Vol. 40, No. 1, pp. 67–71, 2001

Chemotherapy doses are sometimes reduced because of obesity in patients. This study examines the effect of parameters reflecting the body size, body weight and height, body mass index (BMI), and body surface area (BSA) on the depth of the blood leukocyte nadir in breast cancer patients receiving adjuvant chemotherapy, when drug dosing was based on the BSA. Three hundred and forty patients with node positive breast cancer without distant metastases were treated with 6 cycles of adjuvant postoperative CMF (cyclophosphamide 600 mg/m^2, methotrexate 40 mg/m^2, and 5-fluorouracil 600 mg/m^2 i.v. every 3 weeks). Patients within the highest BMI had the highest leukocyte nadir values (Spearman correlation coefficient 0.3, $p < 0.001$). A high body weight and a large BSA were also associated with high leukocyte nadirs. We conclude that when the blood leukocyte nadir is used as a surrogate marker for the drug effect, obese patients receiving intravenous CMF have higher leukocyte nadirs than the lean ones. Therefore, the drug doses should not be reduced because of obesity, and even when obese patients are treated according to the scheduled doses they may remain slightly underdosed.

Received 9 May 2000
Accepted 6 September 2000

Obesity is common in women with breast cancer. Several studies have found an association between obesity and poor prognosis in breast cancer (1–7). Obesity may cause changes in the pharmacokinetics of some drugs, since the excess body mass of obese patients contains more adipose tissue than the lean body mass, which may lead to an altered distribution of hydrophilic and lipophilic drugs (8). Obesity may also cause changes in the plasma protein binding of highly protein-bound drugs and in their renal clearance, and fatty infiltration of the liver related to obesity may cause changes in oxidative metabolism of drugs. In one small study on 16 female patients with breast cancer, the plasma elimination half-life of cyclophosphamide was found to be the longer the higher the body weight, and cyclophosphamide clearance the smaller the higher the body weight when normalized to the body surface area (9). These findings suggest that cyclophosphamide disposition is altered in patients with increased body weight. Because cyclophosphamide is a prodrug that is non-toxic to most tumor cells in culture and needs to be metabolized in the liver to 4-hydroxycyclophosphamide and in tissues to active species such as phosphoramide mustard, these findings suggest that obesity may be associated with less effective production of the active metabolites of cyclophosphamide.

Cyclophosphamide is a main contributor to the haematological toxicity of the CMF regimen (cyclophosphamide, methotrexate, and 5-fluorouracil) (10). There is a tendency among oncologists to reduce cytotoxic drug doses in obese patients based on an ill-defined assumption that dosing in relation to actual body weight puts obese patients at a higher risk for toxicity than the non-obese ones. Moreover, in many dosing schedules doses are capped for patients with a BSA higher than 2.0 m^2. Yet, there is evidence from three studies performed in breast cancer, non-small-cell lung cancer, and non-Hodgkin lymphoma that obese patients do not experience more haematological toxicity than lean patients (11–13), and in some series patients with low leukocyte nadirs during chemotherapy have had generally favourable disease-free survival, suggesting that some patients with high leukocyte nadir values may have remained underdosed (14). In the present study we investigated the associations between the body size related parameters and haematological toxicity in a series of breast cancer patients treated with adjuvant CMF.

 ISSN 0284-186X

MATERIAL AND METHODS

Three hundred and sixty-eight pre- and perimenopausal women with primary, histologically verified pT1-4 node-positive breast cancer, who had no distant metastases at presentation (M0), received postoperative adjuvant CMF in the Department of Oncology, Helsinki University Hospital between 1987 and 1993. Twenty-eight patients were excluded from analyses because of cancer progression during adjuvant CMF (n = 10), fewer than 4 CMF cycles were given (n = 9), or information about the body size parameters (n = 8) or the leukocyte nadir values were missing (n = 1), which left 340 patients eligible for analysis. These 340 patients form the basis of the present study, although 6 further patients had missing data on the relative drug dose intensity, and were excluded from these analyses. The median age was 44 (range, 23 to 65). Staging was done according to the International Union Against Cancer Tumour-Node-Metastasis Classification (15). Staging investigations included clinical investigation, liver enzyme chemistry, chest x-ray, ultrasound examination of the liver, and bone scintigraphy. The characteristics of the cancers are shown in Table 1.

All patients underwent total mastectomy or breast-conserving surgery combined with axillary nodal dissection. Adjuvant chemotherapy consisted of 6 cycles of cyclophosphamide (600 mg/m^2), methotrexate (40 mg/m^2), and 5-fluorouracil (600 mg/m^2) administered intravenously on day 1 of the cycle, at 3-week intervals; 339 patients underwent postoperative locoregional irradiation, and 59 (17%) received adjuvant tamoxifen. The majority of patients who received radiotherapy were irradiated to the regional lymph nodes and the ipsilateral thoracic wall, or to the remaining breast with a linear accelerator (45 to 50 Gy given in 18 to 25 fractions) after the second or the third cycle of chemotherapy, or after 6 cycles of chemotherapy.

Table 1

Breast cancer characteristics (n = 340)

	n (%)
Tumour size	
≤2 cm	136 (40)
2.1–5 cm	163 (48)
> 5 cm	35 (10)
Missing	6 (2)
No. of positive nodes	
1–3	225 (66)
> 3	103 (30)
Missing	12 (4)
Oestrogen receptor	
Positive	180 (53)
Negative	116 (34)
Missing	44 (13)
Progesterone receptor	
Positive	180 (53)
Negative	111 (33)
Missing	49 (14)
Tumour histology	
Ductal	295 (87)
Lobular	35 (10)
Other or missing	10 (3)
Age	
Median (range)	44 (23–65) years

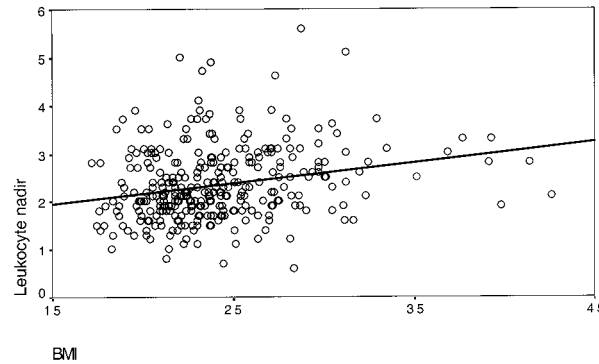

Fig. 1. Association between the lowest leukocyte nadir measured during adjuvant CMF therapy and the body mass index (BMI), leukocyte nadir = 0.043 × BMI + 1.32.

The white blood cell counts, haemoglobin, and platelets were monitored during chemotherapy, and were measured one day before drug infusion and approximately on day 16 of each cycle (SD, 4.7). The lowest leukocyte value during chemotherapy was recorded as the nadir value. The body size parameters (body weight and height, and body surface area (BSA)) had been determined when starting chemotherapy and were extracted from the hospital records. Body mass index (BMI) was calculated by dividing body weight by the squared value of body height (kg/m^2). Patients were considered to be mildly obese if BMI was over 25 kg/m^2 and markedly obese when over 30 kg/m^2. The median body weight was 64 kg (range, from 44 to 119 kg), height 1.65 m (range, from 1.49 to 1.82 m),

Table 2

Leukocyte nadir values according to the body size parameters

Parameter (in tertiles)	Leucocyte nadir (×10^9/L)	p-value*
BMI (kg/m^2)		
<22	2.1	
22–25	2.3	
>25	2.6	<0.001
BSA (m^2)		
<1.64	2.2	
1.64–1.75	2.4	
>1.75	2.4	0.004
Body weight (kg)		
<60	2.2	
60–68.5	2.4	
>68.5	2.4	<0.001
Body height (cm)		
<163	2.4	
163–167	2.3	
>167	2.3	0.3

Table 3

Dose intensities of cyclophosphamide, methotrexate, and 5-fluorouracil of the scheduled doses according to the body mass index (BMI) grouped as tertiles

Dose intensity	BMI <22 kg/m^2	BMI 22–25 kg/m^2	BMI >25	p-value
Cyclophosphamide (%)	86	87	87	0.72
Methotrexate (%)	89	93	89	0.74
Fluorouracil (%)	85	87	86	0.69

BSA 1.7 m^2 (range, from 1.4 to 2.3 m^2), and BMI 23.4 kg/m^2 (range, from 17.2 to 42.6 kg/m^2). Thirty-four percent (n = 115) of the patients were mildly obese (BMI 25 to 30 kg/m^2) and 8.2% (n = 27) markedly obese (BMI over 30 kg/m^2).

The patients were followed-up at 3- to 4-month intervals after chemotherapy for the first 2 years and thereafter at 6-month intervals for at least 5 years. After the fifth year of follow-up the control visits were performed once a year. The control examinations included clinical investigation and blood chemistry, and staging examinations were repeated only if recurrence was suspected. Median follow-up time was 68 months (range, 5 to 126 months).

The associations between the body size parameters and blood leukocyte counts were measured by computing the non-parametric Spearman correlation coefficient resulting from non-normal distributions. The associations between body size parameters and leukopenia, body size parameters and dose intensity and body size parameters and dose were also tested in a non-parametrically using a Kruskall-Wallis test. Frequency tables were analysed using the χ^2 test. A multivariate linear regression model was used to test the relationship between age, the leukocyte nadir, the BMI, and the drug dose. The Kaplan-Meier method was used to estimate survival distributions for disease-free survival (DFS) and the 2-sided log-rank test was used to measure the statistical significance of differences in DFS (body size parameters were divided by median). All p-values are 2-tailed.

RESULTS

The median of the lowest leukocyte nadirs measured during CMF therapy was 2.2×10^9/L (range, from 0.6 to 5.6×10^9/L). Patients with a high BMI had higher leukocyte nadirs than lean patients (Spearman correlation coefficient 0.3, $p < 0.001$). High leukocyte nadirs were also associated with high body weight and large body surface area, but not with body height (Table 2). Although there was a general tendency for patients with a high BMI to have higher leukocyte nadirs during CMF therapy, variation in the depth of the leukocyte nadir was substantial even between patients with a similar BMI (Fig. 1).

The dose intensities of cyclophosphamide, methotrexate and fluorouracil as calculated mg/m^2/week were similar in BMI tertiles during the entire CMF therapy indicating that the higher nadirs found in the obese patients were not due to more frequent dose reductions performed among obese women (Table 3). Cyclophosphamide doses were reduced by more than 10 mg (about 1%) during the entire therapy in 187 (55%) patients.

Body weight tends to increase with age, and patients in the lowest BMI tertile were found to be somewhat younger (median age, 42; range, from 23 to 65) than those with an intermediate BMI (median, 44; range, 28 to 64) or a high BMI (median, 46; range, from 27 to 62, Spearman correlation coefficient 0.2 ($p < 0.001$) between age and BMI). Therefore, we entered the BMI, the cyclophosphamide dose given during the cycle preceding the lowest leukocyte nadir (as a continuous variable as mg/m^2), and age in a multivariate linear regression model using the lowest leukocyte nadir measured during chemotherapy as the dependent parameter. Despite adjusting for age and the cyclophosphamide dose, the association between the BMI and the leukocyte nadir was still highly significant ($p < 0.001$). We also investigated the association between the lowest leukocyte nadir during chemotherapy and the BMI in a subgroup of patients where all patients had received a roughly similar milligram dose of cyclophosphamide per cycle (1000 to 1100 mg, n = 121), and found that a high BMI is associated with a high leukocyte nadir in this subgroup of patients, too (Spearman correlation coefficient 0.25, $p < 0.001$).

The drug doses in the present series were calculated on the basis of BSA, and to test whether the higher leukocyte

Table 4

Cyclophosphamide doses given calculated as mg/m^2, mg/kg, and mg/BMI according to the body mass index (BMI) during the CMF cycle when the lowest blood leukocyte nadir was obtained

Dose as	BMI <22 kg/m^2	BMI 22–25 kg/m^2	BMI >25	p-value
mg/m^2	557	564	556	0.62
mg/kg	16.1	15.0	13.3	<0.001
mg/BMI	44.1	40.8	35.7	<0.001

nadirs among the obese women could be explained by a lower milligram dose per kilogram received during the cycle when the lowest nadir was reached, we calculated the cyclophosphamide dose per kilogram given during the nadir cycle in the BMI tertiles. The cyclophosphamide doses given as calculated per the body weight were lower in obese patients than in the lean patients, and a similar result was obtained when the cyclophosphamide doses given were adjusted for the BMI (Table 4). Scattergrams showing the associations between the lowest leukocyte nadir and the ratio of the cyclophosphamide dose in milligrams given preceding the nadir and the BMI, body weight, and BSA and are shown in Fig. 2. The respective

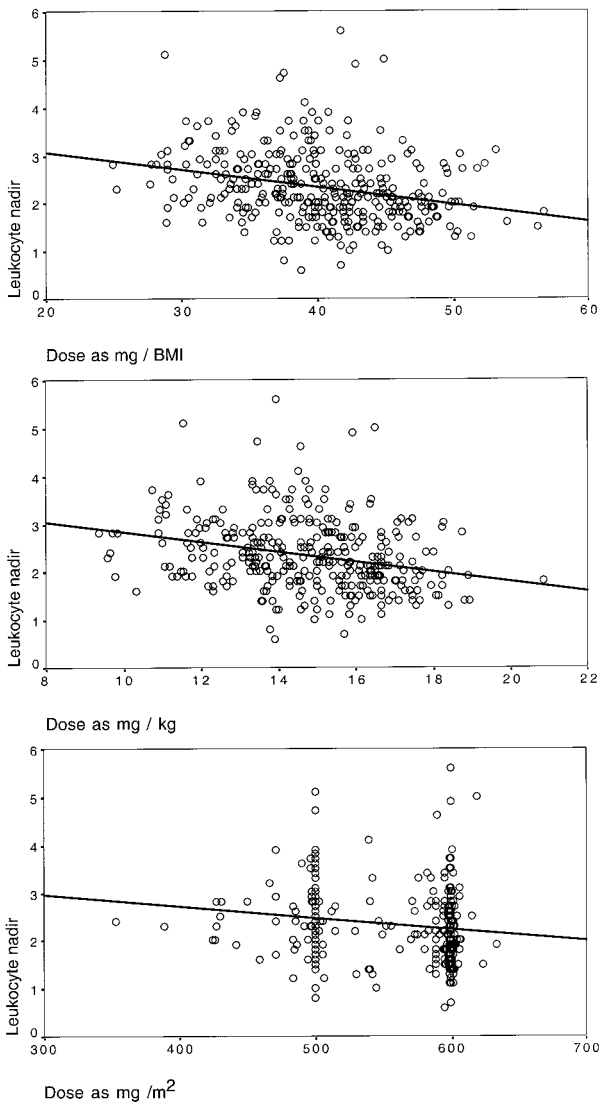

Fig. 2. Association between the lowest leukocyte nadir and cyclophosphamide dose as given as mg/BMI, leukocyte nadir = $-0.036 \times$ mg/BMI $+ 3.79$ (the upper panel), as given as mg/kg, leukocyte nadir = $-0.1 \times$ mg/kg $+ 3.89$ (the middle panel), and as given as mg/m^2, leukocyte nadir = $-0.002 \times$ mg/m$^2 + 3.67$ (the bottom panel).

Spearman correlation coefficients were -0.32 for the ratio of the cyclophosphamide dose and BMI ($p < 0.001$), -0.31 for the ratio of the dose and body weight ($p < 0.001$), and -0.20 for the ratio of the cyclophosphamide dose and BSA ($p < 0.001$).

No association was found between body weight, height, BMI, or BSA and disease-free survival or overall survival in a univariate survival analysis ($p > 0.1$ for all comparisons).

DISCUSSION

Chemotherapy toxicity in relation to body weight has been addressed in only a few studies. Some oncologists lower doses for obese patients because they assume that obese patients are at a higher risk for greater toxicity (11, 16). We found that obese patients do not have more leukopenia than the non-obese patients when the chemotherapy doses were similar with respect to dose intensity calculated as mg/m^2/week. Somewhat unexpectedly, obese patients had less leukopenia than non-obese patients, although variation in the depth of the leukocyte nadir between individuals with a similar BMI were substantial. One possible explanation for less leukopenia in obese patients is decreased conversion of cyclophosphamide to active cytotoxic metabolites by hepatic cytocrome P-450 enzymes because of pathophysiological changes in the liver caused by obesity (9). Obese patients also received less cyclophosphamide as calculated per kilogram of the body weight during the chemotherapy cycle when the lowest leukocyte nadir occurred (Table 4).

We used a low leukocyte nadir as a surrogate marker for drug effect in the present study. Drug effect should not, however, be confused with clinical benefit. In two large, prospective randomized trials that accrued a total of 4853 patients, increase of intravenous cyclophosphamide dose from the standard 600 mg/m^2 to as high as 2400 mg/m^2 per cycle given in combination with 60 mg/m^2 doxorubicin resulted in greater overall toxicity, and increased frequency of severe infections and septic episodes without survival benefit in adjuvant chemotherapy of breast cancer (17, 18). Hence, the increased drug effect and the resulting lower leukocyte nadirs obtained with high cyclophosphamide doses were not associated with clinical benefit in these studies, but only with an increased frequency of adverse effects. On the other hand, smaller than the standard doses of cyclophosphamide, doxorubicin, and fluorouracil have resulted in poorer outcome as compared with the standard doses in the adjuvant setting (19). Similarly, when the standard doses of cyclophosphamide (600 mg/m^2), methotrexate (40 mg/m^2) and fluorouracil (600 mg/m^2) were compared to doses reduced by 50% (300 mg/m^2, 20 mg/m^2, and 300 mg/m^2, respectively) in treatment of metastatic breast cancer, the patients treated with the standard doses had a higher response rate (30% vs. 11%)

and significantly longer median survival (15.6 vs. 12.8 months) as compared with those treated with the reduced doses (20). Taken together, these findings suggest that the use of higher than the standard cyclophosphamide doses should be reserved for clinical trials only, but smaller than the standard doses should not be used routinely. Therefore, reductions of the standard doses based on obesity are probably best avoided during adjuvant CMF therapy.

Chemotherapy drug doses are commonly adjusted using the BSA, but this has been criticized. BSA standardizes poorly for the interpatient variation in pharmacokinetics of many cytotoxic drugs. Pharmacokinetic parameters do not appear to correlate with BSA for the majority of anticancer drugs, with a few exceptions (16, 21, 22). The findings of the present study also suggest that dose calculation based on BSA may not be optimal, although the median differences in the leukocyte nadirs between obese and non-obese patients were small.

We conclude that when the blood leukocyte nadir is used as a surrogate marker for the drug effect and cyclophosphamide, methotrexate, and 5-fluororacil doses are calculated based on the BSA, obese patients have somewhat higher leukocyte nadirs than non-obese patients. Therefore, the drug doses should not be reduced in obese patients receiving intravenous CMF as adjuvant therapy for breast cancer. In fact, when obese patients are treated according to the scheduled drug doses of cyclophosphamide, methotrexate, and 5-fluorouracil, obese patients may remain slightly underdosed.

ACKNOWLEDGEMENTS

We thank Klaus Olkkola, MD and Tiina Saarto, MD for valuable comments, and Finska Läkarsällskapet for financial support.

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