Body Composition as an Independent Determinant of 5-Fluorouracil–Based Chemotherapy Toxicity

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Abstract

Purpose: Evidence suggests that lean body mass (LBM) may be useful to normalize doses of chemotherapy. Data from a prospective study were used to determine if the highest doses of 5-fluorouracil (5-FU) per kilogram LBM would be associated with dose-limiting toxicity in stage II/III colon cancer patients treated with 5-FU and leucovorin.

Experimental Design: Toxicity after cycle 1 was graded according to National Cancer Institute Common Toxicity Criteria, version 2.0. Muscle tissue was measured by computerized tomography. An extrapolation to the LBM compartment of the whole body was employed.

Results: Mean values of 5-FU/LBM of the entire population were different in terms of presence or absence of toxicity ($P = 0.036$). A cut point of 20 mg 5-FU/kg LBM seemed to be a threshold for developing toxicity ($P = 0.005$). This observation was pertinent to women (odds ratio, 16.73; $P = 0.021$). Women in this study had a relatively low proportion of LBM relative to their body surface area.

Conclusion: Our study shows that low LBM is a significant predictor of toxicity in female patients administered 5-FU using the convention of dosing per unit of body surface area. We conclude that variation in toxicity between females and males may be partially explained by this feature of body composition.

5-Fluorouracil (5-FU) is a potent anti-metabolite used to treat a variety of solid tumors, and it is a well-established form of chemotherapy for colorectal cancer (1). The Mayo regimen of bolus 5-FU and leucovorin is associated with significant myelosuppression, mucositis, and diarrhea. In one study, 35% of patients had significant toxicity with patients experiencing dose reductions, therapy discontinuations, hospitalization, and even death (2). Attempts have been made to identify clinical variables to predict patients at risk for severe toxicity (3), but an approach for individualizing 5-FU dosing remains unclear.

Interpatient variation in toxicities can arise from differences in target protein(s) expression, drug metabolism, and excretion. Disparate metabolism and excretion of anticancer drugs in turn can be due to environmental, physiologic, and genetic factors. Our hypothesis is that a physiologic factor, heterogeneous body composition of cancer patients, and, specifically, relative amounts of lean and adipose tissue compartments contribute to interpatient variation in toxicities. We propose that the size of lean and fat compartments relate to the pharmacokinetic properties of a drug, as hydrophilic drugs distribute into the lean compartment, whereas lipophilic drugs distribute into the fat compartment.

Currently, for most chemotherapy, dose is determined using body surface area (BSA). The practice originated from observations that basal metabolic rates scaled between species according to weight. Early investigators used BSA to estimate an appropriate starting dose for an anticancer drug for phase I studies based on preclinical animal studies (4). BSA dosing became established in clinical settings in part by dogma and not due to studies showing that pharmacokinetic interpatient variation correlated to BSA. Investigators have argued that dose adjustment of chemotherapy by BSA does not reduce toxicity (4–8).

There is growing evidence to suggest that lean body mass (LBM) may be better for normalizing doses of drugs that distribute in and are metabolized by the LBM compartment (5, 6, 9–11). This compartment is comprised of metabolic tissues, such as the liver and kidney (5, 12), and intracellular and extracellular water and bone. 5-FU is relatively hydrophilic and is expected to distribute into and to be metabolized by the LBM (5).

We used data from a prospective study designed to determine if thymidylate synthase gene polymorphisms are associated with 5-FU/leucovorin efficacy and toxicity. The polymorphism data will be presented separately. We hypothesized that conventional dosing of 5-FU/m^2 of BSA would result in a significant variation in effective 5-FU dose/kg of LBM, and that

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the highest doses of 5-FU/kg LBM would be associated with dose-limiting toxicity (DLT) in patients with high-risk stage II/III colon cancer treated with adjuvant 5-FU/leucovorin.

Materials and Methods

Patients and study

This analysis was done in conjunction with separate determinations of pharmacogenetic predictors of toxicity to adjuvant 5-FU/leucovorin chemotherapy in colon cancer, a prospective study carried out at the Cross Cancer Institute, Edmonton, Alberta, Canada. Inclusion criteria included histologically proven high-risk stage II (defined as T_3 or T_4, N_0, M_0; high-risk features were perforation, obstruction, lymphovascular or perineural invasion, high grade, aneuploidy, and/or signet ring cell histology) or stage III (T_{any}, N_{1-2}, M_0) colon cancer; complete resection of the primary; WHO performance status <2; no prior chemotherapy; and adequate bone marrow reserve (neutrophils $\geq 1.5 \times 10^9$ cells/L and platelets $\geq 100 \times 10^9$ cells/L). Exclusion criteria included known dihydropyrimidine dehydrogenase deficiency. The study was approved by the Alberta Cancer Board Research Ethics Board. Ninety-five patients completed the original study, and 62 patients (30 females, 32 males) with useful computerized tomography (CT) images were selected for the present analysis.

Treatment plan

Patients were planned to receive six 28-day cycles of daily 5-FU (425 mg/m^2) and leucovorin (20 mg/m^2) by i.v. bolus for 5 days. BSA was calculated using the Mosteller formula: BSA (m^2) = [(height (cm) $\times$ weight (kg)] / 3,600)$^{1/2}$.

Toxicity assessment

Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria, version 2.0. Patient toxicity assessments were obtained by a diary provided before each cycle of chemotherapy, and this was reviewed by a research nurse. Toxicity profiles were obtained for all six cycles of 5-FU/leucovorin, but only toxicities experienced in cycle 1 were used for this study. Only cycle 1 was used because some patients had their dose modified after cycle 1. As such, data obtained in cycle 2 and/or following cycles would not be valid for those patients. Assessment of neutropenia was based upon blood work done during cycle 1 and before cycle 2. Primary analysis compares rates of grade 3/4 toxicity, dose delays, dose reductions, and combinations of all three as DLT (any grade 3/4 toxicity, dose delay, or reduction), defined as overall toxicity, with body composition measures.

Body composition measurements

Anthropometric measurements. Weight and height were recorded during visits according to standard methods. Weight was measured with a medical balance beam scale, and height was measured with a stadiometer. Body mass index was calculated as weight (kg) / height (m^2).

Image analysis. CT has proven to be accurate for measuring human body composition (13, 14). Regional adipose tissue (visceral and s.c.) and muscle tissue were measured by CT, which had been done previously for diagnostic purposes. Images selected were on average 37 days before or after initiation of cycle 1 (SE, 3.35). There were no interventions (such as surgery) between the dates of the CT scan and of chemotherapy that would substantially alter body composition.

The third lumbar vertebrae (L3) was chosen as a landmark, and four consecutive slices extending from L3 to the iliac crests were assessed to measure cross-sectional area of muscle and adipose tissue as described by Shen et al. (15). The average value for four images was computed for each patient. Images were analyzed using Slice-O-matic software V4.3 (Tomovision). Using pre-established thresholds of Hounsfield units, specific tissues were identified and quantified: -29 to 150 for skeletal muscle (14), -190 to -30 for s.c. and intermuscular adipose tissue (14), as well as -50 to 150 for visceral adipose tissue (16). Subsequently, cross-sectional areas (cm^2) of respective tissues were computed for each image. Abdominal muscle area was extrapolated to whole-body LBM

Table 1. Patient characteristics and rates of toxicity

Variables	Females	Males	Total	*P*
No. patients	30	32	62	—
Patient characteristics				
Age	58.0 ± 10.3	62.6 ± 9.0	60.3 ± 9.9	0.062
Weight (kg)	68.8 ± 17.1	86.5 ± 19.7	77.9 ± 20.4	<0.001*
Height (m)	1.6 ± 0.1	1.7 ± 0.1	1.7 ± 0.1	<0.001*
Body mass index (kg/m^2)	26.7 ± 6.4	28.5 ± 5.4	27.6 ± 5.9	0.212
BSA (m^2)	1.7 ± 0.2	2.0 ± 0.3	1.9 ± 0.3	<0.001*
Total muscle cross-sectional area at L3 (cm^2)	120.0 ± 23.3	173.5 ± 28.4	147.6 ± 37.3	<0.001*
Total fat cross-sectional area (cm^2) at L3 †	301.8 ± 220.5	381.9 ± 204.0	346.9 ± 213.2	0.161
Muscularity (cm^2/m^2)	46.5 ± 7.3	57.5 ± 8.5	52.1 ± 9.7	<0.001*
Fatness (cm^2/m^2) †	118.5 ± 90.5	125.5 ± 64.3	122.5 ± 76.2	0.734
Whole-body LBM (kg) ‡	38.2 ± 7.6	55.7 ± 9.3	47.2 ± 12.2	<0.001*
Incidence of toxicity§				
Mucositis	2 (6.7%)	1 (3.1%)	3 (4.8%)	0.488
Diarrhea	1 (3.3%)	7 (21.9%)	8 (12.9%)	0.057
Neutropenia	13 (43.3%)	8 (25%)	21 (33.9%)	0.207
Other grade 3/4 toxicity	7 (23.3%)	2 (6.3%)	9 (14.5%)	0.097
Dose delay/reduction	19 (63.3%)	16 (50%)	35 (56.5%)	0.365
Overall toxicity‖	20 (66.7%)	18 (56.3%)	38 (61.3%)	0.418

NOTE: Data reported as mean ± SD for patient characteristics.
*Significant differences between males and females (Student's *t* test).
† For this variable, *n* = 25. Five obese female patients had substantial s.c. adipose tissue such that a part was outside the limits of image (cut off). Data for these individuals are thus not included.
‡ Calculated from regression equation: whole-body lean tissue mass determined by dual-energy X-ray = [L3 muscle measured by CT (cm^2) - 3.2459] / 3.0583.
§ Rates of 5-FU toxicity (grade 3/4), dose delay/reduction, and overall toxicity (DLT).
‖ Any grade 3 or 4 toxicity or dose delay/dose reduction.

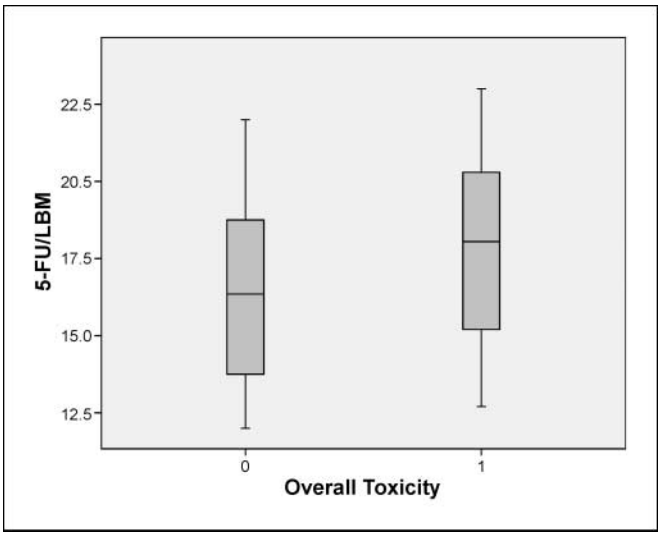

Fig. 1. Relationships between 5-FU dose/kg of LBM and incidence of toxicity for stage II and III colon cancer patients (n = 62). 0, toxicity absent (n = 24); 1, toxicity present (n = 38). P = 0.022 comparing 5FU/LBM between toxicity absent and toxicity present group (Student's t test).

using a formula that related abdominal muscle with whole-body LBM measured by dual-energy X-ray absorptiometry. This is similar to approaches reported by Shen et al. (15) for healthy adults, except that our regression equations were derived from metastatic colorectal or lung cancer patients. The formula used was whole-body LBM (kg) = [L3 muscle measured by CT (cm^2) - 3.2459] / 3.0583 (r = 0.94).[3]

Statistical analysis. Data were expressed as mean ± SD. The significance of the association between two variables was assessed by Fisher's exact test and comparisons between two means by Student's t test for unpaired data. All P values were two sided, and level of significance was $P < 0.05$. 5-FU dose was expressed as amount of 5-FU per estimated LBM (mg 5-FU/kg LBM), and we evaluated associations of this variable with toxicities. Toxicity was modeled as a function of 5-FU/LBM and age as a prognostic factor using logistic regression. Statistical analysis was done using SPSS (SPSS for Windows, version 14.0, SPSS).

Results

Table 1 describes the patients' demographics. Muscle and adipose tissue values, measured by CT scans are reported as total muscle and total fat cross-sectional area at L3 (cm^2) and muscularity and fatness [total muscle area and total fat area divided by patient's height squared (cm^2/m^2)], a way of normalizing the value by height.

Five women had CT scans that had s.c. adipose tissue out of the scan viewing field; therefore, total adipose tissue was not considered for these patients. According to body mass index classification, 29.7% of patients were obese (including 2.2% morbidly obese), 30.8% overweight, 33.0% normal weight, and 4.4% underweight.

Neutropenia was the most common toxicity (Table 1). With the exception of diarrhea, all symptoms were more frequent in women. Other grade 3/4 toxicities reported were hand-foot syndrome, nausea, rash, diverticulitis, vomiting, alopecia, febrile neutropenia, and fatigue. Approximately 56% of patients had treatment delays or dose reductions. Overall, 67% of women and 56% of men had DLT.

The planned dose of 5-FU was 425 mg/m^2, and the administered dose was within ~5% of the target dose. Patients had a very wide range of body composition, and when 5-FU dose was divided by estimates of LBM derived from CT scans, the dose/LBM actually varied 2-fold (from 12 to 23 mg/kg LBM; Fig. 1). In women, the 5-FU dose/kg LBM varied from 12.8 to 23 mg/kg LBM and for men from 12 to 20.1 mg/kg LBM (Fig. 2). When the population was analyzed according to the presence or absence of DLT, the mean value of 5-FU/kg LBM was significantly different between patients who did or did not have DLT. Patients who had DLT had a mean of 5-FU/kg LBM of 17.9 versus 16.3 mg/kg in patients who did not (P = 0.036, Student's t test). Mean values of 5-FU/BSA and 5-FU/body weight were not different between patients who did or did not have toxicity (P = 0.384 and P = 0.132, respectively).

A cut point of 20 mg 5-FU/kg LBM seemed to be a threshold for developing overall toxicity. Fourteen patients had a 5-FU/kg LBM higher than this value, and a DLT was experienced by 13 (93%) of these patients compared with 48 patients at or below this cut point in whom only 25 (52%) had DLT (P = 0.005). Logistic regression supported a cut point of 20 mg/kg as a significant predictor of toxicity (odds ratio, 16.75; P = 0.013). Age was also a significant predictor of toxicity; however, this effect was much smaller than that of LBM (odds ratio, 1.06; P = 0.047). We used the median 5-FU/kg LBM of the whole population as a cut point and compared rates of toxicity above and below the median (17.2 mg/kg), but, in this case, only a trend towards significance was found (P = 0.096).

When men and women were analyzed separately, the cut point of 20 mg/kg for the women was, again, the threshold for development of DLT. Twelve women of 13 with a 5-FU dose/kg LBM higher than this level experienced DLT. A dose ≤20 mg

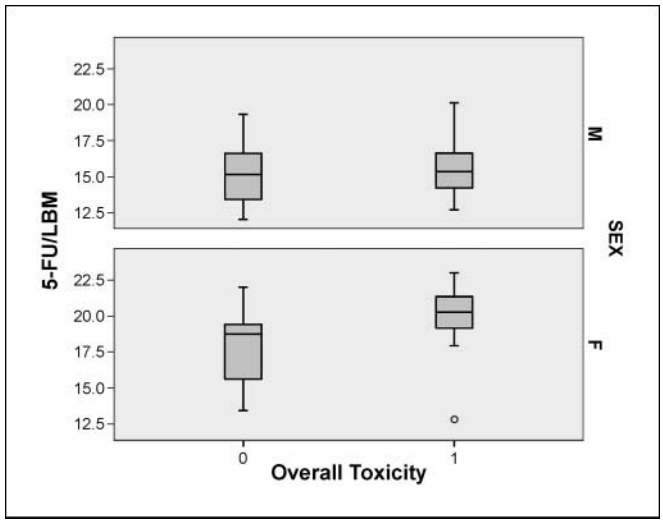

Fig. 2. 5-FU dose/kg LBM for men (n = 32) and women (n = 30) with respect to toxicity. 0, toxicity absent (14 men and 10 women); 1, toxicity present (18 men and 20 women); M, men; F, women. °, outlier. Mean 5-FU/LBM was significantly different for toxicity absent and toxicity present group (P = 0.012 and $P < 0.001$, respectively, Student's t test).

[3] Mourtzakis M, et al. A critical comparison of computed tomography, dual-energy X-ray absorptiometry, and bioelectrical impedance approaches to quantification of body composition in cancer patients. Submitted for publication.

Table 2. Comparison of females who received ≤20 or >20 mg/kg of 5-FU per kg LBM

Variables	Cut point ≤20 mg/kg 5-FU/LBM	Cut point >20 mg/kg 5-FU/LBM	*P*
No. patients	17	13	—
Age	57.9 ± 9.5	58 ± 11.7	0.977
Weight (kg)	68.4 ± 17.2	69.3 ± 17.5	0.896
Height (m)	1.6 ± 0.1	1.6 ± 0.1	0.935
Body mass index (kg/m^2)	26.3 ± 5.5	27.1 ± 7.6	0.752
BSA (m^2)	1.7 ± 0.2	1.7 ± 0.2	0.943
Total muscle cross-sectional area at L3 (cm^2)	128.6 ± 26.3	108.8 ± 12.2	0.011*
Total fat cross-sectional area (cm^2) at L3 †	292.9 ± 200.9	315.3 ± 257.9	0.819
Muscularity (cm^2/m^2)	49.5 ± 7.0	42.5 ± 5.7	0.005*
Fatness (cm^2/m^2) †	112.5 ± 76.4	127.6 ± 112.4	0.716
Whole-body LBM (kg) ‡	41.3 ± 8.3	35.0 ± 3.9	0.011*
5-FU dose mg/kg LBM	16.1 ± 2.3	21.2 ± 0.9	<0.001*

*Significant differences (Student's *t* test).
† Missing values for five patients (see Table 1 legend).
‡ Calculated from regression equation: whole-body lean tissue mass determined by dual-energy X-ray = [L3 muscle measured by CT (cm^2) - 3.2459] / 3.0583.

5-FU/kg LBM was received by 17 women, and 8 of experienced DLT. Logistic regression showed that 20 mg/kg as cutoff for 5-FU/kg LBM was a significant predictor of overall toxicity (odds ratio, 16.73; $P = 0.021$) for women, even when controlling for age (odds ratio, 1.06; $P = 0.198$). Results did not change if the median of 5-FU/kg LBM (19.4 mg/kg) for women was applied as a cut point for investigating incidence of toxicity ($P = 0.0446$). Women with a value of 5-FU/kg LBM >20 mg/kg had significantly lower total muscle cross-sectional area and LBM (-15%) and higher 5-FU/kg LBM (+ 24%) compared with women below the cut point ≤20 mg/kg (Table 2). BSA did not differ between the two groups. It seems that women had a relatively low proportion of LBM relative to BSA. By contrast, only one man received a dose of 5-FU >20 mg/kg lean tissue (Fig. 2). This may be accounted for the tendency of men to be more muscular than women (Table 1). Because the number of men receiving a dose of 5-FU above 20 mg/kg was small, it was not possible to use logistic regression to test LBM as a predictor of toxicity in men. Comparing men above and below the median 5-FU/LBM (15.4 mg/kg) showed no differences in toxicity ($P = 0.638$).

Discussion

Our study shows that LBM is a significant predictor of 5-FU toxicity. Over 60% of patients developed DLT, and we analyzed the incidence of toxicity in relation to the estimated dose of 5-FU/kg LBM. The 2-fold range of 5-FU/kg LBM observed in our analysis provides evidence that LBM is extremely variable in cancer patient populations. Moreover, when comparing the average value of 5-FU/kg LBM between subgroups of patients that did or did not experience toxicity, the difference was significant, and the same association was not seen with BSA. For our study, a cut off point of 20 mg 5-FU/kg of LBM was a predictor of 5-FU toxicity (odds ratio, 16.75). Because the majority of patients with low ratio of LBM to BSA were female, we conclude that variation in terms of toxicity by sex may be partially explained by this feature of body composition.

Our results add to and are in concordance with other studies. Aslani et al. (6) studied 31 patients treated with cyclophosphamide, methotrexate, and 5-FU chemotherapy using BSA dosing. They found a 28-fold increase in the relative risk of grade 3/4 neutropenia in multivariate analysis if a patient's LBM was <89% of age and sex-adjusted norms. Although methods of body composition analysis (whole-body nitrogen counting) and units of expression of the data were different in the study of Aslani et al. (6) than those used here, the overall conclusions of our studies are identical.

Gusella et al. (9) reported that fat-free mass (LBM without i.m. fat and fat in cell membranes) and total body water (intracellular and extracellular water) were better predictors of 5-FU pharmacokinetics (clearance and volume of distribution) than BSA or total body weight. Although 5-FU is thought to be metabolized in the liver, the observation that fat-free mass was a good predictor of 5-FU clearance suggests that 5-FU metabolism takes place in other body compartments as well.

Our data suggest a distinct gender effect in 5-FU toxicity relating to differences in body composition in men and women. Previous studies have suggested that women experience more 5-FU toxicity than men (1, 17–19), although they failed to provide a consistent explanation for this difference. An important proportion of the toxicity observed here in women was associated with a low LBM and hence a higher dose of 5-FU/LBM than men. Although 43% of women in our study received >20 mg 5-FU/kg LBM, only 3% of men received this dose. Because only one man was above 20 mg 5-FU/kg LBM, we were unable to investigate if men respond in a similar manner as women do with respect to doses above this level. Several mechanisms have been proposed, and one suggestion is that 5-FU metabolism may be different in women (17). Dihydropyrimidine dehydrogenase is believed to play a major role in 5-FU catabolism. Some authors have suggested that women are prone to dihydropyrimidine dehydrogenase deficiency (18, 19), but a larger study by Etienne et al. (20) reported that dihydropyrimidine dehydrogenase deficiency is a rare event. 5-FU clearance has also been suggested to be lower in women than in men (21, 22).

Both dual-energy X-ray and CT/magnetic resonance imaging analysis are widely regarded to constitute the gold standard in human body composition analysis (23). Amounts of adipose

and lean tissues in single lumbar abdominal images correlate very well with whole-body lean and adipose tissues (15). Image analysis is both a highly precise and a clinically expedient measure of body composition. Using this approach, we have obtained data to suggest that differences in toxicities between patients are partially due to variation in LBM. Furthermore, differences in toxicity between men and women with respect to 5-FU may be due to differences in LBM. Our study and previous research (6, 9) suggest that 5-FU dose normalization to LBM may be a better way to individualize 5-FU chemotherapy and therefore prevent excess toxicity than the current convention of normalizing the dose to BSA. This concept awaits verification through prospective testing of drug dosing schedules per kilogram LBM.

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