Sarcopenia as a Determinant of Chemotherapy Toxicity and Time to Tumor Progression in Metastatic Breast Cancer Patients Receiving Capecitabine Treatment

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Abstract

**Purpose:** Body composition has emerged as an important prognostic factor in cancer patients. Severe depletion of skeletal muscle (sarcopenia) and, hence, of overall lean body mass may represent an occult condition in individuals with normal or even high body weight. Sarcopenia has been associated with poor performance status, 5-fluorouracil toxicity, and shortened survival in cancer patients. Here, we prospectively studied patients with metastatic breast cancer receiving capecitabine treatment in order to determine if sarcopenia was associated with a higher incidence of toxicity and a shorter time to tumor progression (TTP).

**Experimental Design:** Fifty-five women with metastatic breast cancer resistant to anthracycline and/or taxane treatment were included. Skeletal muscle cross-sectional area at the third lumbar vertebra was measured by computerized tomography, and sarcopenia was defined using a previously published cutoff point. Toxicity was assessed after cycle 1 of treatment, and TTP was determined prospectively.

**Results:** Approximately 25% of patients were classified as sarcopenic, and this feature was seen in normal weight, overweight, and obese individuals. Toxicity was present in 50% of sarcopenic patients, compared with only 20% of nonsarcopenic patients (P = 0.03), and TTP was shorter in sarcopenic patients (101.4 days; confidence interval, 59.8-142.9) versus nonsarcopenic patients (173.3 days; confidence interval, 126.1-220.5; P = 0.05).

**Conclusion:** Sarcopenia is a significant predictor of toxicity and TTP in metastatic breast cancer patients treated with capecitabine. Our results raise the potential use of body composition assessment to predict toxicity and individualize chemotherapy dosing.

There has been recent interest in exploring relationships between body composition, specifically proportions of lean and fat tissues, with cancer incidence and cancer outcomes. We have showed a wide degree of variability of muscularity and hence of lean body mass (LBM), in contemporary cancer patient populations (1, 2). Low relative muscularity or low overall LBM are apparently related to toxicity and survival (1, 2). Nevertheless, data are limited in scope in terms of the drugs studied, the types of patients/tumor groups, and outcomes that have been evaluated.

Current evidence suggests that LBM may be a better measure for normalizing doses of drugs that are distributed in and metabolized in lean tissues, compared with body surface area (BSA) alone (1–8). The lean tissue compartment is composed of metabolic tissues such as the liver and kidney (3, 9), intracellular and extracellular water, and skeletal muscle (which contributes a high proportion of overall LBM). The condition of low muscle mass is termed sarcopenia, and has been studied mainly in patients with nonmalignant diseases, or geriatric populations (9, 10). Sarcopenia was initially defined as a level of muscle mass 2 SD below sex-specific norms for young adults (11); however, we recently determined sex-specific cutoffs for cancer patients, based on mortality risks (2). Whether sarcopenia is a predictor of other clinical outcomes such as treatment response or tumor progression remains unknown.

Here, we extended our analysis (1) to capecitabine, a produg of 5-fluorouracil (5-FU) developed to improve tolerability and antitumor biological effect (12). Capecitabine is used as a single agent in metastatic breast cancer unresponsive to anthracycline- and/or taxane-based regimens (13). The standard Food and Drug Administration (FDA)-approved capecitabine dose (1,250 mg/m² twice daily) is associated with unacceptable toxicity in approximately one-third of breast cancer patients...
The study by Hennessy et al. (13) led to many breast cancer medical oncologists adopting a lower capecitabine dose of 1,000 mg/m² twice daily as opposed to the dose in the FDA-approved product monography. Therefore, as in with the majority of anticancer drugs, individualizing capecitabine dose by BSA does not reduce interpatient variability in toxicity (15). Capecitabine is a highly water soluble drug, and therefore, it is expected to distribute into and to be metabolized in the lean compartment (12).

Our purpose was to add to the base of evidence on sarcopenia and treatment toxicity and to further investigate clinical outcomes in patients with metastatic breast cancer, using time to tumor progression (TTP) as a study end point. This is the first study evaluating relationships between body composition on chemotherapy toxicity and TTP in patients with metastatic breast cancer. We hypothesized that an increased risk of toxicity, as well as a shorter TTP, would be observed in sarcopenic patients.

Patients and study design. The present study was conducted in the context of an investigation of capecitabine and thymidylate synthase gene polymorphisms, in which we prospectively evaluated toxicity and efficacy outcomes after capecitabine therapy for metastatic breast cancer. This study was carried out at the Cross Cancer Institute, from September 2002 to January 2005. The polymorphism data will be presented separately (16).

Eligible women had metastatic breast cancer, had failed anthracycline and/or taxane treatment, and were to receive capecitabine for the first time. Inclusion criteria included the following: an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, 2, or 3; creatinine of <1.5 times the upper limit of normal; an aspartate aminotransferase or alanine aminotransferase of ≤350 IU/L; bilirubin of ≤500 μmol/L; and adequate bone marrow reserve with a neutrophil count of ≥1.0 × 10⁹/L. Pretreatment albumin levels, estrogen receptor status, and human epidermal growth factor receptor status (HER-2) status were determined. Patients were excluded if they had hypersensitivity to 5-FU, known dihydropyrimidine dehydrogenase deficiency, active uncontrolled bacterial or viral infections, or were pregnant or lactating. The study was approved by the Alberta Cancer Board Research Ethics Board and informed consent was obtained from all participants.

One hundred and twenty-seven women participated in the original study (16); and 66 had computerized tomography (CT) images that met criteria for analysis. Patients who did not have evaluable scans either had no scans on record (n = 37), or a scan >30 d from treatment initiation (n = 4), and were, therefore, not included in our analysis. Based on pharmacogenetic data from the original study, nine patients presented with four thymidylate synthase enhancers (TSER*3G/TSER*3G). This genotype confers a protective effect from capecitabine toxicity (17), and was not expected to have toxicity regardless of their body composition type (16). Therefore, these patients were excluded from the present analysis. In addition, two patients who were missing genotype data were also excluded. Therefore, 55 women with metastatic breast cancer were selected for the present study (Fig. 1A).

Treatment plan. The initial capecitabine dose was selected by the treating oncologist from 1 of 2 options: either the FDA-approved dosing of 1,250 mg/m² twice daily p.o. for 14 d every 3 wk, or 1,000 mg/m² twice daily on the same schedule. Because capecitabine is associated with significant toxicity, physicians were allowed to use their clinical discretion to adjust doses based on patient tolerability and clinical response (13, 14).
judgment to start patients on 1,000 mg/m² if they considered that to be indicated. This was not due to prior toxicity but to a clinical assessment of each study participant. Only eight patients were treated at the FDA-approved dose. BSA was calculated using the Mosteller formula \[ \text{BSA (m²)} = \left(\frac{\text{height (cm)} \times \text{weight (kg)}}{3.6000} \right)^{1/2}. \]

**Toxicity and efficacy 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 in person by a research nurse after each cycle. Toxicity profiles were obtained for all cycles, and first-cycle toxicities were analyzed for this study because patients who had toxicity (defined as ≥grade 2) had dose reductions for subsequent cycles. Capecitabine treatment was interrupted (dose delays or reductions) if patients developed grade 2 or higher toxicity. Therefore, toxicity is hereby defined as incidence of any toxicity of ≥grade 2.

Reported toxicities were palmar-plantar erythrodysesthesia or hand-foot syndrome, nausea, vomiting, stomatitis, or neutropenia. Site of metastasis was divided into four major groups: respiratory tract, liver, bone, and other metastasis (stomach, ovary, brain, and mediastinum). Sites of tumor progression represent prognostic indicators for this disease. Toxicity was modeled as a function of sarcopenia, age, performance status, and albumin levels as prognostic factors using logistic regression. TTP is defined as the number of days of tumor remission after cycle 1 and was analyzed by univariate and multivariate analysis, including major established predictors of outcome of advanced cancer reported in the literature: site of tumor recurrence/progression, albumin levels, estrogen receptor status, HER-2 status, age, and performance status. Methods of Kaplan-Meier were used to determine effects of each variable on TTP. Log-rank tests were used to compare curves of each variable. Variables known to influence TTP were entered into a multivariate Cox proportional hazards model, with 95% confidence intervals (CI) for estimated relative risk calculated. Statistical analysis was completed using SPSS (SPSS for Windows, version 16.0: SPSS).

### Results

**Patient characteristics and incidence of toxicity.** Patient characteristics are described in Table 1. Patients presented with a wide range of BMI, LBM, and skeletal muscle index. Estimated LBM and BSA were only weakly related in this patient population (Fig. 2A). As a consequence, the administered dose of capecitabine was highly variable when expressed per kg of LBM, ranging over twice (67.4-137 mg/kg LBM).

A comparison between sarcopenic and nonsarcopenic patients is shown in Table 2. Among 55 patients, 14 (25.5%) had sarcopenia. Patients with sarcopenia received a higher amount of capecitabine dose per unit of LBM and also presented with a higher prevalence of toxicity ([50% or 7 of 14]; compared with nonsarcopenic patients [20% or 8 of 41]; \( P = 0.03 \); Table 2; Fig. 2B). Significant differences in ECOG status, age, weight, height, BMI, BSA, estrogen receptor, and HER-2 status were not observed between sarcopenic and nonsarcopenic patients.

Prevalence of sarcopenia was not different between patients receiving the FDA dose compared with the alternate dose. Two (14%) sarcopenic patients received the FDA dose and 12 (86%) received the alternate dose whereas in the nonsarcopenic group, 6 (15%) patients received the FDA dose and 35 (85%) received the alternate one (\( P = 1.000 \); Fisher’s exact test).

Common toxicities observed included hand-foot syndrome, diarrhea, stomatitis, nausea, and vomit. Only one patient presented with febrile neutropenia. Diarrhea and stomatitis were more commonly observed among sarcopenic patients (\( P = 0.01 \) and 0.008, respectively; Table 2).

**Sarcopenia as a predictor of toxicity and TTP.** Prevalence of toxicity was significantly higher in sarcopenic compared with

### Table 1. Patient characteristics (N = 55)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mean ± SD (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>54.8 ± 10.4 (37-80)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.0 ± 5.5 (18.2-46.1)</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.8 ± 0.2 (1.4-2.3)</td>
</tr>
<tr>
<td>Muscle cross-sectional area (cm²)</td>
<td>11.4 ± 19.5 (67.5-165.7)</td>
</tr>
<tr>
<td>Lumbar skeletal muscle index (cm²/m²)</td>
<td>44.2 ± 7.1 (26.4-59.4)</td>
</tr>
<tr>
<td>Estimated LBM (kg)*</td>
<td>40.3 ± 5.8 (26.3-55.8)</td>
</tr>
</tbody>
</table>

*Calculated from regression equation: whole lean body mass (kg) = 0.30 × [skeletal muscle at L3 using CT (cm²)] + 6.06;*17.

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nonsarcopenic patients. Variables known to relate to chemotherapy toxicity (age, BSA, performance status, and albumin levels) were further modeled using logistic regression. Sarcopenia was the only significant predictor of toxicity (hazard ratio, 4.1; \(P = 0.04\)) even after controlling for performance status, albumin, and age. Sarcopenia and BSA were not modeled together because these variables are correlated. Correlations between albumin and skeletal muscle index were also weak.

After \(~ 630\) days after cycle 1, all patients had documented tumor progression. Median TTP was shorter for sarcopenic patients (62 days CI, 47.3-76.7) compared with those non-sarcopenic (105 days CI, 52.3-157.7; \(P = 0.05\) log-rank test; Fig. 3). TTP was not influenced by age, BSA, performance status, site of metastasis, and HER-2 receptor status. Factors influencing TTP were subsequently modeled for 52 patients (3 missing values) using a multivariate Cox proportional hazards model (Table 3). Sarcopenia emerged as a significant predictor of shorter TTP (hazard ratio, 2.6; \(P = 0.01\)), independent of albumin, site of metastasis, and estrogen receptor status.

Discussion

Our study shows that sarcopenia is a significant predictor of toxicity and TTP in women with metastatic breast cancer receiving capecitabine treatment. Sarcopenic patients were three times more likely to present toxicity compared with nonsarcopenic patients, suggesting that variation in terms of toxicity is partially explained by this feature of body composition.

As shown by the wide range of muscularity in this population, body composition is extremely variable and was clearly related to the toxicities experienced by this cohort, whereas BSA, ECOG performance status, and serum albumin levels were not predictive of toxicity. Sarcopenia was not present exclusively in underweight patients; in fact, 98% of our cohort would not be considered underweight by commonly accepted criteria (BMI \(\leq 18.5\) kg/m²). Therefore, sarcopenia is an occult condition that can be present in patients with any body weight and BMI. Moreover, depletion of lean tissue in sarcopenic patients was considerable. It is notable that the estimated LBM of sarcopenic patients studied here (34 ± 3.3 kg) is much lower than values reported for patients regarded as cachectic \(\text{i.e., 49.0 kg (23) and } 43.4\text{ kg (24)}\).

Our results are concordant with other studies. Aslani et al. (7) studied 31 patients treated with cyclophosphamide, methotrexate, and 5-FU using BSA-based dosing. They reported a 28-fold increase in the relative risk of grade 3 and 4 neutropenia (using 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) differed in the study of Aslani et al. (7) from our study, both show that chemotherapy toxicity is strongly and inversely related to muscularity.

We hypothesize that the relationship between body composition and capecitabine toxicity is primarily due a pharmacokinetic effect. Capecitabine is a prodrug that is metabolized to 5-FU. Consistent with our findings, Gusella et al. (6) reported that fat-free mass (LBM plus bone tissue) and total body water were better predictors of 5-FU pharmacokinetics (clearance and volume of distribution) than BSA or total body weight.

We previously reported that patients with colorectal cancer may have low LBM relative to their BSA (1). A consequence of low LBM would be a low volume of distribution of cytotoxic chemotherapy drugs, and our earlier study suggested that higher doses of 5-FU/kg LBM were associated with a higher incidence of overall toxicity (1).

For the present analysis, we further conjectured that a previously used sex-specific cutpoint to define sarcopenia is also predictive of toxicity. Moreover, patients with sarcopenia presented with higher doses of capecitabine/kg LBM. For a person with sarcopenia, a lower volume of distribution of a drug would result in higher concentrations in a shorter period of time; therefore, this person would be less physiologically able to clear the drug from the systemic circulation.

Explanations for the observation that sarcopenia is associated with TTP are unclear. In this study, we showed that the presence of sarcopenia was associated with a significantly shorter TTP (hazard ratio, 2.6; CI 1.2-5.6). TTP is an important clinical end point, as it indicates when a patient requires treatment changes, and correlates with overall survival in women.

**Fig. 2.** A, relationship between total lean body mass and body surface area for metastatic breast cancer patients. B, prevalence of dose limiting toxicity between patients with metastatic breast cancer with (50%) and without (19.5%) sarcopenia \((n = 55)\), \(P = 0.039\), Fisher’s exact test.
receiving chemotherapy for metastatic breast cancer (25). Sarcopenia has been associated with unfavorable clinical outcomes such as increased length of hospital stay, increased incidence of infections for hospitalized patients, and mortality, among others (26–28). Whether muscle catabolism directly promotes tumor progression (29), or whether the impaired immunologic responses that accompany sarcopenia (30) contribute to shortened TTP, remains speculative. Kadar et al. (31) reported a positive and significant association between the amount of muscle mass and recurrence-free survival in patients with lung cancer receiving radiation therapy. The authors used in vivo neutron activation analysis to measure body protein content, an indirect measure of muscle mass in the body. According to the authors, changes in body protein content preceded changes in body weight and albumin levels. We speculate that a very aggressive or advanced underlying disease is associated with low muscle mass, which in turn is a prognostic factor for the disease, as well as a predictor of toxicity.

Another unclear point is whether toxicity-related follow up changes in treatment schedule could have been responsible for shorter TTP. Although we can only speculate on this discussion, patients’ intolerance to the drug may have contributed to a decrease in TTP as a reflection of a lower dose and therefore lower likelihood of response. Conversely, although these patients received a high dose in cycle 1, their response rate was still poor (shorter TTP). We believe that the presence of toxicity was a reflection that patients were overdosed based on their small LBM and that a decrease in the dose for sarcopenic patients would have translated into an adequate exposure of the biological dose with acceptable

### Table 2. Comparisons between patients with and without sarcopenia

<table>
<thead>
<tr>
<th></th>
<th>Sarcopenic (n = 14; 25.5%)</th>
<th>Nonsarcopenic (n = 41; 74.5%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>7 (50.0%)</td>
<td>8 (20%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Absent</td>
<td>7 (50.0%)</td>
<td>33 (80%)</td>
<td></td>
</tr>
<tr>
<td>ECOG performance status*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No performance impairment (scores 0-1)</td>
<td>9 (64%)</td>
<td>25 (65%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Performance impairment (scores 2-3)</td>
<td>5 (36%)</td>
<td>14 (35%)</td>
<td></td>
</tr>
<tr>
<td>Estrogen receptor status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>8 (57%)</td>
<td>31 (76%)</td>
<td>0.31</td>
</tr>
<tr>
<td>Negative</td>
<td>6 (43%)</td>
<td>10 (24%)</td>
<td></td>
</tr>
<tr>
<td>HER-2 status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>3 (21%)</td>
<td>15 (37%)</td>
<td>0.35</td>
</tr>
<tr>
<td>Negative</td>
<td>11 (79%)</td>
<td>26 (63%)</td>
<td></td>
</tr>
<tr>
<td>Characteristics mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>56.6 (11.4)</td>
<td>54.1 (10.1)</td>
<td>0.43</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>65.6 (11.4)</td>
<td>71.4 (16.7)</td>
<td>0.23</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.6 (0.1)</td>
<td>1.6 (0.1)</td>
<td>0.11</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.6 (4.0)</td>
<td>27.8 (5.7)</td>
<td>0.06</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.7 (0.2)</td>
<td>1.8 (0.2)</td>
<td>0.42</td>
</tr>
<tr>
<td>Albumin</td>
<td>39.8 (4.9)</td>
<td>39.1 (4.5)</td>
<td>0.60</td>
</tr>
<tr>
<td>Lumbar skeletal muscle index (cm²/m²)</td>
<td>35.0 (3.3)</td>
<td>47.4 (5.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Whole body lean mass (kg)</td>
<td>34.0 (3.3)</td>
<td>42.5 (5.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mg capcitabine/kg LBM</td>
<td>104.2 (16.1)</td>
<td>86.9 (13.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Toxicity prevalence b</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>3 (21%)</td>
<td>4 (8%)</td>
<td>0.35</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4 (29%)</td>
<td>1 (2.4)</td>
<td>0.01</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>5 (36%)</td>
<td>2 (4.9%)</td>
<td>0.008</td>
</tr>
<tr>
<td>Nausea</td>
<td>3 (21%)</td>
<td>3 (7%)</td>
<td>0.17</td>
</tr>
<tr>
<td>Vomit</td>
<td>1 (7%)</td>
<td>1 (2.4)</td>
<td>0.45</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>1 (7.1%)</td>
<td>0</td>
<td>0.25</td>
</tr>
</tbody>
</table>

*ECOG performance status score missing for one patient (n = 54).

†Albumin status missing for 2 patients (n = 53).

Grade 2 or higher toxicity (associated with dose delays or reductions).

Fig. 3. Comparison of time to tumor progression between sarcopenic and non-sarcopenic patients (P = 0.05).
side effects. Future prospective studies can be used to test these hypotheses. CT is increasingly used to evaluate human body composition (18, 32) and is routinely used to evaluate tumor response in cancer patients. Using CT image analysis and a previously validated cutpoint to identify sarcopenia (2) has provided data to suggest that differences in toxicities between patients are partially due to variation in muscularity. Determining an optimal cutpoint for toxicity prediction will require additional prospective studies with larger sample sizes.

Our results highlight the potential use of body composition assessment to improve toxicity risk and to individualize drug dosing in a population of patients with advanced cancer of the breast. This concept warrants formal validation in studies evaluating drug dosing based on pretreatment body composition analysis.

Disclosure of Potential Conflicts of Interest

M.B. Sawyer, research support, advisory board, Roche. J.R. Mackey, advisory board, Roche. The other authors disclosed no potential conflicts of interest.

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