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The Impact of Skeletal Muscle on the Pharmacokinetics and Toxicity of 5-Fluorouracil in Colorectal Cancer

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Abstract

Purpose—Great heterogeneity exists in the ability of adults with cancer to tolerate chemotherapy. Variability in body composition may affect rates of metabolism of cytotoxic agents and contribute to the variable chemotherapy toxicity observed. The objective of this exploratory study was to examine the association of low skeletal muscle, commonly known as sarcopenia, on the pharmacokinetics (PKs) of 5-fluorouracil (5FU) in patients receiving FOLFOX for colorectal cancer.

Methods—We performed a secondary analysis of a completed multicenter trial that investigated PK-guided 5FU dosing in patients receiving mFOLFOX6 +/- bevacizumab for colorectal cancer. Cycle 1 PK samples were obtained 2–44 hours after the start of the 5FU infusion (steady-state).

Results—No significant differences in first cycle 5FU area-under-the-concentration-time-curve (AUC)s were found between sarcopenic and non-sarcopenic patients (17.3 vs. 19.3 AUC, $p=0.43$). Patients with grade 3/4 toxicity had a higher dose of 5FU per kg lean body mass (LBM) (105 vs. 93 mg/kg, $p=0.06$), most notably for hematological toxicities (110 vs. 94 mg/kg, $p=0.002$); however, no correlation between the dose/LBM and 5FU AUC was found.

Conclusions—Although our results did not confirm the impact of low skeletal muscle on PKs of 5FU, further research exploring the impact of body composition on chemotherapy PKs and related toxicities is warranted with the potential for alternative dosing strategies in sarcopenic patients in order to reduce unnecessary toxicities while maintaining efficacy.

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Keywords

sarcopenia; pharmacokinetics; skeletal muscle index; cancer

Introduction

Heterogeneity exists in the ability of adults with cancer to tolerate chemotherapy. In metastatic colorectal cancer (CRC), chemotherapy is complicated by the high incidence and large individual variability in toxicity, particularly in older adults [1, 2]. To minimize the risk of adverse outcomes, there is a critical need to understand the causes of such variability in chemotherapy toxicity.

Differences in body composition may underlie some of the heterogeneity in chemotherapy toxicity by altering chemotherapy distribution, metabolism, and clearance [3]. A wide distribution of lean body mass (LBM) is seen for any given body weight, which is not accounted for by conventional chemotherapy dosing by body surface area (BSA) [3]. In aging, loss of skeletal muscle and increases in adiposity result in a lower LBM relative to overall body weight, thus potentially causing a lower volume of distribution and higher drug concentrations. Low muscle mass, commonly known as sarcopenia, is highly prevalent in adults with cancer [4]. Low muscle mass in adults with CRC is associated with an increased risk for chemotherapy toxicity and shorter survival [5, 6]. Low LBM relative to BSA may account for increased toxicities observed in sarcopenic patients [3, 5].

Our primary objective was to explore the association of sarcopenia (low muscle mass) and 5-fluorouracil (5FU) pharmacokinetics (PKs) in patients receiving FOLFOX ± bevacizumab for CRC. We hypothesized patients with sarcopenia would have higher 5FU exposure, measured as area-under-the-concentration-time-curve – (AUC), and increased chemotherapy toxicities.

Materials and Methods

We performed a secondary analysis of a multicenter trial of PK-guided 5FU dosing in patients receiving mFOLFOX6 +/- bevacizumab for CRC [7]. All patients received mFOLFOX6 at cycle 1: oxaliplatin 85 mg/m² over 2 hours, leucovorin 200–400 mg/m² over 2 hours, 5FU 400mg/m² bolus, 5FU 2,400 mg/m² over 46 hours (via a battery operated pump) with or without bevacizumab. Cycle 1 PK samples were obtained 2–44 hours after the start of the 5FU infusion (steady-state). AUC analysis was conducted by Myriad Genetics, Inc. via nanoparticle-based immuno-assay. The target AUC range of infusional 5FU was 20–25 mg × h/L [7]. Toxicity was measured using the NCI CTCAE v3.0 during cycles 1–4.

Abdominal computed tomography (CT) scans performed as part of usual care prior to chemotherapy administration were used to examine body composition. The transverse section at the L3 vertebral level was identified and extracted for analysis using automated image segmentation software [8]. The L3 landmark was used as it has been identified as the strongest predictor of whole body fat and fat-free mass when compared to dual-energy x-ray

absorptiometry (DXA) [9, 10]. The software recognizes muscle tissue based on density thresholds and provides an unbiased estimation of the cross-sectional skeletal muscle area (SMA). Images were reviewed and corrected for accuracy by trained study personnel. Measured SMA was normalized for square height to calculate a skeletal muscle index (SMI) (cm^2/m^2) using the following formula: $(\text{skeletal muscle area}-\text{cm}^2) / (\text{patient height}-\text{m}^2)$. Sarcopenia was defined using gender and BMI cut-offs from Martin *et al*; men (BMI <25): SMI <43 cm^2/m^2 ; men (BMI ≥25): SMI <53 cm^2/m^2 ; women (regardless of BMI): SMI <41 cm^2/m^2 [6]. We chose these specific cutoffs as they were derived from a large population of patients with gastrointestinal cancers and their frequent use in the oncology literature. We estimated total LBM using the following formula: $[\text{LBM (kg)} = 0.30 \times [\text{skeletal muscle at L3 using CT (cm}^2\text{)}] + 6.06]$ [5].

This study was approved by the IRB at the University of North Carolina (IRB-16-0124) and study procedures were in accordance with the ethical standards of the responsible committee on human experimentation.

Statistical Analyses

For the primary objective, incidence of chemotherapy toxicity and 5FU AUCs were compared between sarcopenic and non-sarcopenic patients using two group t-tests and Fisher's exact tests. We also examined the association between 5FU dose per estimated LBM (mg infusional 5FU/kg LBM) [5] with severe toxicities. Poisson regression models with a robust variance estimator were used to estimate unadjusted relative risks with 95% confidence intervals. All analyses were conducted using SAS v9.4 statistical software (Cary, NC).

Results

Of the 70 patients from the original study, we obtained CT images for 25 participants. The mean age was 59 years, 52% female, and 80% Caucasian (Table 1). The mean dose of 5FU per kg LBM was 90 mg/kg (range 50–154 mg/kg). The average first cycle AUC for 5FU was 18 (range 7–31), and the majority of patients were under the target therapeutic range (64% with AUC <20).

Twelve patients were sarcopenic (48%). Although sarcopenic patients had a statistically higher dose of 5FU/LBM compared to non-sarcopenic patients (110 vs 87.5 mg/kg, $p=0.0087$), no significant differences in first cycle 5FU AUCs were found (17.3 vs. 19.3 AUC, $p=0.43$).

Eleven patients (44%) had grade 3/4 toxicity, including 28% with hematologic and 28% with non-hematologic, during the first four cycles. Sarcopenic patients were more likely to experience grade 3/4 toxicities (50% vs 39%, $p=0.70$). Patients with grade 3/4 toxicity also had a higher average dose of 5FU/LBM (105 vs. 93 mg/kg, $p=0.058$), which was more pronounced in hematological toxicities (110 vs. 94 mg/kg, $p=0.002$) than non-hematological (100 vs 98 mg/kg, $p=0.75$) (figure 1). There was no difference in 5FU/LBM between AUC categories (figure 1).

In an unadjusted model, for every 10 mg/kg increase in the dose of 5FU/LBM the relative risk of any grade 3/4 toxicities was 1.15 (95% CI 1.0–1.3), 1.29 (95% CI 1.1–1.5) for grade 3/4 hematological toxicity, and 1.04 (95% CI 0.8–1.3) for grade 3/4 non-hematological toxicities.

Discussion

In this exploratory study, sarcopenic patients with CRC trended towards higher incidence of severe grade 3/4 toxicities, however there was no difference in first cycle 5FU AUCs. Higher doses of infusional 5FU per LBM were associated with more severe chemotherapy toxicity, but not with 5FU AUC. Although our findings were not able to confirm the impact of low skeletal muscle on PKs, we believe this warrants further evaluation given the growing evidence that LBM-dosing may be superior to conventional BSA-dosing for drugs that are distributed and metabolized in lean tissue [3]. This is likely particularly relevant for older adults in whom sarcopenia is highly prevalent [11].

Variability in 5FU PKs is widely recognized [7]; this is partially explained by genotype differences in dihydropyrimidine dehydrogenase (DPD) [12], the metabolizing enzyme of 5FU, and differences in distribution and clearance based on age, sex, organ function, and diet [13]. The limited sample size and limited PK analysis (which did not include peak concentration, clearance, or volume of distribution) of this exploratory analysis preclude definitive conclusions about the contribution of these factors to our findings.

Changes in body composition as a result of aging and cancer cachexia are not accounted for by traditional BSA dosing and may contribute to the variability in treatment outcomes in cancer [3]. Explicit evaluation of the impact of muscle mass on chemotherapy drug levels is needed to better understand the relationship between sarcopenia and chemotherapy toxicity and may lead to an individualized dosing strategy that reduces toxicity while maintaining efficacy.

Compliance with Ethical Standards

The initial study from which our data was collected was funded by an investigator-initiated research grant to Howard L. McLeod from Myriad Genetics, Inc. (NCT01164215). The authors confirm no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the prior study.

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Figure 1.

Differences in the dose (mg) of infusional 5FU per lean body mass (kg) in patients with and without grade 3/4 all toxicities (A), grade 3/4 heme toxicity (B), and grade 3/4 non-heme toxicity (C). The last figure demonstrates the differences in 5FU dose/LBM for the patients within the various AUC ranges (D).

Table 1

Patient characteristics

	Total Sample (n=25)
Age , mean (range)	59 (34–79)
Sex , n(%)	
Male	12 (48)
Females	13 (52)
Race , n(%)	
White	20 (80)
Black	3 (12)
Other	2 (8)
Cancer Stage , n(%)	
Stage II	2 (8)
Stage III	11 (44)
Stage IV	12 (48)
Body Composition Measures , mean (range)	
Skeletal Muscle Area (cm ²)	139 (80.6–194)
Skeletal Muscle Index (cm ² /m ²)	47.3 (28.5–67.6)
Body Mass Index (kg/m ²)	26.9 (17.3–37.9)
Lean Body Mass (kg)	47.7 (30.2–64.3)
Body Surface Area (m ²)	1.93 (1.45–2.28)
Sarcopenic *, n(%)	
Yes	12 (48)
No	13 (52)
Sarcopenic and Obese , n(%)	
Yes	0 (0)
No	25 (100)
Toxicities , n(%)	
Any grade 3–4 toxicity	11 (44)
Hem grade 3/4 toxicity	7 (28)
Non-hem grade 3/4 toxicity	7 (28)
Cycle 1 5FU Pharmacokinetics	
Average AUC, mean(range)	18.3 (7.0–31)
AUC <20, n(%)	16 (64)
AUC between 20–25, n(%)	5 (20)
AUC > 25, n(%)	4 (16)

* based on Martin *et al* 2013 gender based cutoffs.

Abbreviations: 5FU, 5-fluorouracil; AUC, area-under-the-concentration-time-curve

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