FORCE: Focus on Reducing Dose-Limiting Toxicities in Colon Cancer with Resistance Exercise

Statistical Analysis Plan

NCT03291951

3-9-2022

The intervention will begin within the first weeks of adjuvant chemotherapy and will continue until 2 weeks past the last chemotherapy cycle (i.e., "end-of-study"). The intervention will include twice-weekly training sessions.

DESCRIPTION OF PRIMARY ENDPOINTS

1.1 Chemotherapy completion rates

Relative dose intensity (RDI) will be calculated for each chemotherapy agent as well as average relative dose intensity (ARDI), which considers all chemotherapy agents in a regimen. We will examine differences in overall RDI for each chemotherapy agent and the ARDI across regimens between the RT group and the UC group.

RDI will be calculated as Delivered dose intensity (DDI) / Standard dose intensity (SDI). SDI will be calculated as the starting dose/m2 multiplied by number of planned cycles by total number of days from day 1 of first cycle after randomization to last planned dose of that drug. DDI will be calculated as the sum total of dose/m2 for each of the cycles that occur between randomization and follow-up, divided by total number of days from day 1 of first cycle after randomization to last actual dose of that drug. Calculation of DDI will include missed cycles similar to Weycker's method. Thus, our measure of RDI incorporates dose reduction/modification, treatment delay, and early stoppage.

1.2 Chemotherapy-associated toxicities

We will examine differences in chemotherapy tolerance through patient-reported outcomes. The NCI Patient-Reported Outcomes-Common Terminology Criteria for Adverse Events (PRO-CTCAE) is a patient-reported outcome measurement system developed to characterize the frequency, severity, and interference of symptomatic treatment toxicities. Participants completed a customized 9-item PRO-CTCAE questionnaire around the initiation of each chemotherapy cycle reporting on the following symptomatic toxicities: nausea, vomiting, diarrhea, shortness of breath, hand-foot syndrome, numbness in hands and feet, pain, muscle aches and fatigue. Each symptom had 1-3 questions that asked about frequency and/or severity, and/or interference. Answers from those questions were then categorized as none, mild, moderate, or severe**,** based on expert consensus of oncologists [1].

STATISTICAL CONSIDERATIONS

2.1 Sample Size

This study intended to randomize 180 colon cancer patients, with 90 in each treatment arm. In the end, due to missing data due to COVID, we randomized 183 participants, 92 to RT and 91 to UC. We expect chemotherapy dosing and completion rates (RDI, ARDI) to be assessed on all participants.

2.2 Analysis of primary endpoints

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All data analyses will be by intent-to-treat. Multiple linear regression will be used to assess the difference between the RT and UC groups in RDI. We will analyze RDI individually for each drug and then across all chemotherapy regimens combined. We will use logistic regression to examine the commonly used cut points < 85% and <70% RDI as outcomes.

We will assess the difference between RT and UC groups in self-reported treatment toxicities in three ways:

A. as a binary variable with yes as the occurrence of any of one of 8 symptoms that are reported as moderate or severe over the course of chemotherapy in RT vs. UC. We will exclude the PRO-CTCAE muscle ache item from the composite score (will be reported separately), since that is believed to be related to the performance of the resistance training intervention. We'll utilize logistic regression for point and interval estimation of odds ratios, RT vs. UC, for any (i.e., one or more) of 8 symptoms reported as moderate severe, for each symptom individually, and finally in groups of similar symptoms, such as gastrointestinal issues;

B. as the number of the 8 symptoms reported as moderate or severe at least once over the course of chemotherapy in RT v. UC (a count ranging from 0-8). We will use Poisson regression with allowance for overdispersion for point and interval estimation of relative differences (rate ratio) in the mean total number of moderate or severe toxicities reported at least once over the course of chemotherapy; and

C. as longitudinal analyses of number of moderate or severe toxicities reported per cycle in relation to randomization arm (RT vs. UC) and time since randomization using Poisson regression with allowance for overdispersion. Generalized estimation equations (GEE) will be used for model parameter estimation to account for within person correlation in repeated measures. The main effect for randomization arm is interpreted as the average treatment effect over the time. Heterogeneity in effect over time will be assessed by inclusion of randomization arm by time-interaction terms.

In addition to treatment arm, each model will include covariates used in the randomization procedure (study site, treatment duration, treatment regimen, gender, stage). Exploratory analyses will examine the impact of including additional (not pre-specified) covariates in estimation of treatment effect, with a focus on variables with chance imbalance in distributions by treatment group. Analyses resulting in an appreciable change in the estimate of between-group differences or increase in precision of the treatment effect will be noted.

We will also conduct analyses stratified by sex, frailty status and duration of the intervention, excluding the strata-variable from the covariate list (i.e., exclude gender in analysis by men and women) by inclusion of appropriate cross product terms in regression models. Exploratory analyses will additionally assess heterogeneity in treatment effect on study outcomes by exercise adherence.

References

1. Basch E, Becker C, Rogak LJ, Schrag D, Reeve BB, Spears P, Smith ML, Gounder MM, Mahoney MR, Schwartz GK, Bennett AV, Mendoza TR, Cleeland CS, Sloan JA, Bruner DW, Schwab G, Atkinson TM, Thanarajasingam G, Bertagnolli MM, Dueck AC. Composite grading algorithm for the National Cancer Institute's Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). Clin Trials. 2021 Feb;18(1):104-114. doi: 10.1177/1740774520975120. Epub 2020 Dec 1. PMID: 33258687; PMCID: PMC7878323.