NWU2015-06-01 Evaluating Intermittent Dosing of Aspirin for Colorectal Cancer Prevention

Katrina Alber, Harvey Murff, Reid Ness, Douglas Seidner, Xiangzhu Zhu, Martha Shrubsole, Mary Beth Tull, Kelly A. Benante, Adrian J. Segura, Kiril Kalinichenko, Lifang Hou, Borko Jovanovic, Gary Della'Zanna, Ellen Richmond, Seema Ahsan Khan, Qi Dai

Background

Despite reductions in the risk of colorectal cancer (CRC) through colonoscopy, it remains the 4th most common cancer in the United States. Most clinical cancer chemoprevention trials investigate consecutive daily dosing regimens, however, long-term use of COX-2 inhibitors, NSAIDs, and aspirin has known cardiovascular toxicity. To address this barrier, this ongoing double-blind placebo controlled randomized trial investigates the effects of an intermittent dosing schedule of aspirin. Intermittent administration of a known, efficacious drug such as aspirin is an innovative approach to explore aspirin's effect as a colorectal cancer chemoprevention agent while reducing the known toxicity associated with a daily dosing regimen.

Research Objectives

Primary Objective

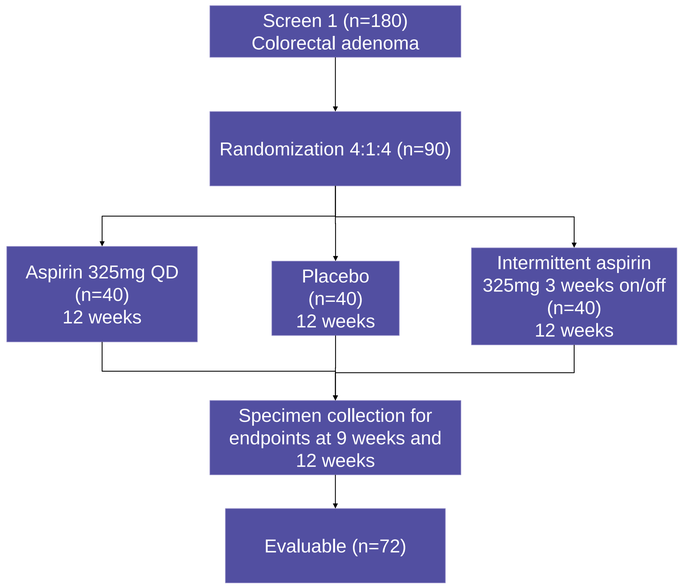
To test for the equivalency of a continuous versus intermittent aspirin schedule, as demonstrated by similar changes in the ratio of cell proliferation to apoptosis in rectal biopsy samples (Ki67 : Bax) over a three-month dosing period.

Secondary Objectives

1. To evaluate the effects of aspirin treatments on:
   - The ratio of cell proliferation (Ki-67)/apoptosis (TUNEL) in rectal biopsies
   - The ratio of cell proliferation (Ki-67)/necroptosis (MLKL) in rectal biopsies
   - Fecal occult blood test (measures adverse events) as measured by stool samples
   - Methylation biomarkers in genes involved in colorectal carcinogenesis, as measured in rectal biopsies
   - Colorectal mucosal nanoscale cellular structural changes measured by partial wave spectroscopy (PWS)
   - Abundance of E. coli and fusobacterium in rectal swabs

2. To evaluate if the effects of aspirin arms may be modified by dietary intake of calcium as measured by the Food Frequency Questionnaire

Methods



Partial Wave Spectroscopy (PWS)

The use of PWS in the evaluation of rectal biopsies in this trial has multiple advantages when compared to Low-coherence Enhanced Backscattering Spectroscopy (LEBS). The LEBS technology requires a rectal biopsy, however, PWS can be performed through a **much less-invasive** cell brushing with a standard cytology brush. While LEBS could potentially be implemented using a fiber optic probe instead of a biopsy, special equipment would need to be stationed in the physician's office to do so. PWS can be performed in a central laboratory on fixed cytology samples, which is **more easily translatable into clinical practice**. In addition, **PWS performs better in CRC biomarker studies** than LEBS technology since it is able to evaluate the most diagnostic cell compartment – the nuclear structure – through imaging of cells. PWS is expected to yield better performance and results than our consortium's previously completed study (NWU 04-2-03) which utilized LEBS.

Statistical analyses will be based on 32 evaluable subjects in each of the two aspirin arms (allowing for drop-outs); we will have 81% power to detect a change in the proliferation : apoptosis ratio of -3.0 to +3.0, based on the standard deviation of similar data from an ongoing trial. Enrollment began in January 2018.

Eligibility

Participants must have a history of colorectal adenoma (any grade), and no history of the following: invasive malignancy in the past two years; chronic renal or liver disease; unstable angina; hemorrhagic stroke or uncontrolled hypertension; anemia; peptic ulcer; gastrointestinal bleeding; active colitis; or inflammatory bowel disease. Participants must not have taken aspirin, other NSAIDs, or COX-2 inhibitors 3 weeks prior to the intervention; alcohol use <2 drinks/day.

Recruitment

Recruitment will occur at **Vanderbilt University Medical Center.**

Personalized Prevention of Colorectal Cancer Trial (PPCCT) is an ongoing R01 randomized trial funded by NCI (R01CA149633; Dai & Yu, PI) that was conducted among 240 colorectal polyp patients. Over the past five years, we have successfully established a candidate pool of patients diagnosed with colorectal adenoma during the recruitment process for the PPCCT. Using an electronic medical record-based approach for initial screening, over 10,000 colorectal polyp patients have been diagnosed at Vanderbilt University Medical Center. 1,033 of these screened patients have submitted a DNA sample and are willing to participate in future studies. Of this group, 739 patients have a history of colorectal adenoma.

Recruitment of African American Participants

The PPCCT database does not contain African American patients, as African Americans are not polymorphic at the genetic locus that is a major aim of the parent study. To address this, 600 African American patients diagnosed with a colorectal adenoma at Vanderbilt University will be contacted by phone, with information about the study mailed to them as a follow-up. We estimate that around 24 African Americans will be willing and eligible to screen.

Funding

This study is funded by contract HHSN2612201200035I from the National Cancer Institute, National Institutes of Health, U.S. Department of Health and Human Services.

Vanderbilt University Medical Center

Robert H. Lurie Comprehensive Cancer Center of Northwestern University