Journal of Geriatric Oncology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Journal of Geriatric Oncology

Challenges of conducting a prospective clinical trial for older patients: Lessons learned from NCCTG N0949 (alliance)

Nadine J. McCleary [a,*,1], Joleen Hubbard [b,1], Michelle R. Mahoney [c], Jeffrey A. Meyerhardt [a], Daniel Sargent [c,2], Alan Venook [d], Axel Grothey [b]

[a] Department of Medical Oncology, Dana-Farber/Partners Cancer Care, Boston, MA, United States
[b] Department of Medical Oncology, Mayo Clinic, Rochester, MN, United States
[c] Alliance Statistics and Data Center, Mayo Clinic, Rochester, MN, United States
[d] Department of Medical Oncology, University of San Francisco, CA, United States

ARTICLE INFO

Article history:
Received 4 May 2017
Received in revised form 14 July 2017
Accepted 14 August 2017
Available online xxxx

Keywords:
Advanced cancer
Advanced colon cancer
Advanced rectal cancer
Older adult
Advanced colorectal cancer
Clinical trial
Elderly
Oxaliplatin
Bevacizumab

ABSTRACT

Objectives: While the risk of developing colorectal cancer increases with age, there are limited prospective data regarding best treatment in the older adult population. We launched a phase III trial to evaluate difference in treatment outcome for older adults (aged ≥70 years) with advanced colorectal cancer. Here we review the challenges faced and reasons for poor accrual to N0949.
Materials and Methods: We describe the conceptualization, development and limited results of N0949, a randomized phase III study of fluoropyrimidine/bevacizumab with or without oxaliplatin (mFOLFOX7 or XELOX) as first line chemotherapy for metastatic colorectal cancer.
Fluoropyrimidine was physician choice (e.g., 5-FU/LV or capecitabine).
Results: Of the projected 380 patients, only 32 patients were enrolled between the study activation in January 2011 until its closure in September 2012. Reasons for poor accrual included eligibility criteria that were too stringent, discomfort with randomizing older patients to regimens of varying intensity without considering their physical fitness, and discomfort with the use of bevacizumab in the older patient population. Several efforts were mounted to design a rationale and age-appropriate study, consider toxicities and varying study practices, and be responsive to stakeholder feedback.
Conclusions: Challenges were experienced in conducting the first prospective phase III study evaluating progression-free survival of older adults with advanced colorectal cancer receiving palliative chemotherapy with fluoropyrimidine/bevacizumab with or without oxaliplatin in the USA. Future efforts to evaluate treatment outcomes in the older adult population should reflect on lessons learned in this large national effort.

1. Introduction

In the United States, older patients (age ≥ 65) only comprise about 30% of patients enrolled in clinical trials, resulting in a lack of data on usage and tolerance of newly developed therapies in this patient population [1]. There have been multiple European metastatic colorectal cancer (mCRC) clinical trials for the older adult population conducted with success [2–6], but clinical trials for this patient population in the United States are lacking.

Reasons for low enrollment are multifactorial [7–10]. Older adults are more prone to have other active medical conditions at the time of cancer diagnosis, leading to poorer functional status that curtails clinical trial eligibility typically requiring robust performance status. To manage concurrent medical conditions, older adults tend to have multiple medications prescribed that may compound the adverse effects of experimental therapies, making it challenging to attribute toxicity. Further, the offering of clinical trials is often a function of the physician treating the patient. This subjectivity introduces potential for physician bias in whether and how a trial is discussed with an older adult. Lastly, clinical trials are typically offered in academic treatment centers that may not be easily accessible for older adults who are often treated in community settings. For these reasons, clinical trials often do not reflect the general oncology population, comprised predominantly of older adults. Consequently, treatment decisions based on clinical trial results are not generalizable to this population. We sought to design a trial to answer a key question regarding treatment of mCRC in older adults, tailored to the needs older adults and accessible at community treatment centers.

* Corresponding author at: Dana-Farber Cancer Institute, 450 Brookline Avenue, Boston, MA 02215, United States.
E-mail address: nj_mccleary@dfci.harvard.edu (N.J. McCleary).
[1] Co-first author.
[2] Post-humous.

http://dx.doi.org/10.1016/j.jgo.2017.08.005
1879-4068/

2. N0949 Development

2.1. Trial Hypothesis and Objectives

The specific hypothesis of North Central Cancer Treatment Group (NCCTG) N0949 was that treatment with oxaliplatin-based chemotherapy plus bevacizumab will result in superior clinical benefit compared to fluoropyrimidine-based chemotherapy plus bevacizumab, as measured by overall survival, in older adults with mCRC. The primary objective of the study was to determine whether the addition of oxaliplatin to a fluouropyrimidine and bevacizumab leads to improved overall survival (OS) among older adults with mCRC. Secondary objectives included comparison of response rates, progression-free survival (PFS), toxicity, and quality of life. If the addition of oxaliplatin did not significantly improve OS, then this patient population could be spared the toxicity of oxaliplatin and still achieve similar survival results with a fluoropyrimidine and bevacizumab alone, potentially preserving physical function for a longer period and improving quality of life.

2.2. Original Trial Design

The trial was originally designed to enroll adults age ≥ 70 years to receive first-line treatment for mCRC. Eligible patients were randomized to either the control (Arm A) or experimental (Arm B) treatment arms. Arm A received a fluoropyrimidine of the provider's choice (5-fluorouracil/leucovorin or capecitabine) plus bevacizumab. Arm B received modified FOLFOX7 or XELOX, plus bevacizumab. Patients were evaluated with CT imaging every 6 weeks. Patients continued their assigned treatment until progression of disease by RECIST version 1.1 criteria, unacceptable toxicity or patient withdrawal.

Eligible patients included those diagnosed with untreated mCRC age ≥ 70 years, ECOG performance status 0–2, life expectancy ≥3 months, able to complete questionnaire(s) by themselves or with assistance, and provide informed written consent. In addition, the following laboratory values were required <14 days prior to randomization: absolute neutrophil count ≥1500/mm^3, peripheral platelet count ≥100,000/mm^3, hemoglobin >9.0 g/dl, total bilirubin ≤1.5× upper limit of normal (ULN), aspartate transaminase <2.5× ULN (<5× ULN for patients with liver involvement), alkaline phosphatase <3× ULN (<5× ULN for patients with liver involvement), Creatinine <1.5× ULN, INR <1.5× ULN unless patients are receiving anti-coagulation therapy. Patients receiving prophylactic anti-coagulation therapy with an agent such as warfarin or heparin are allowed to participate if INR ≤ 3.0, and UPC ratio < 1 or urine dipstick <2+. Those patients with co-morbid systemic illnesses or other severe concurrent disease which would make the patient inappropriate for entry, immunocompromised patients, other malignancy ≤3 years prior to randomization, recurrent disease ≤12 months of completing oxaliplatin-containing adjuvant therapy, creatinine clearance <60 mL/min, symptomatic or untreated brain metastases, class 3+ heart failure, uncontrolled hypertension, major surgical procedure <28 days, hemoptysis, non-healing wound, recent arterial thrombotic event, bleeding diathesis, and ≥ grade 2 peripheral neuropathy were excluded.

We estimated a median OS of 17 months in the control group [11]. Sample size calculations were based on obtaining enough events to achieve 80% power to detect a hazard ratio of 0.81 (an increase in median OS to 21 months in the experimental arm). We estimated an accrual rate of 12 patients per month (25 patients per month for the joint trials), an accrual period of 2.5 years and two years of minimum follow-up. We planned for two interim analyses for superiority of OS (after 33% and 66% of the planned number of events) using O'Brien-Fleming stopping boundaries. This phase III trial was to be monitored twice annually by the NCCTG Data and Safety Monitoring Board (DSMB).

2.3. Correlative Studies

Geriatric assessment was a pivotal focus of the study, introduced for the first time in a randomized trial in colorectal cancer. The cancer-specific geriatric assessment (CGA) tool was developed by Arti Hurria and colleagues within the cooperative group setting to thoroughly review and identify issues in older adults that may affect cancer treatment [12–14]. Details of the CGA metrics and validation studies are published elsewhere [15–17]. The CGA has been shown to predict chemotherapy toxicity for older adults with cancer [18,19]. The CGA has been validated in written format in a multicenter clinical trial [15,20] and validated in a computer format in an individual center trial [16]. Inclusion of the CGA would have served as external validation of the tool specifically within CRC to predict moderate to severe treatment-related toxicity, hospitalization, dose delay or reduction or discontinuation of chemotherapy.

The trial included additional patient-centered correlative studies focused on patient-reported assessment of treatment-related adverse events (PRO-CTAE), neurotoxicity assessment (Neurotoxicity Symptom Experience Diary), as well as assessments of quality of life (QoL) [Fatigue/Uniscale assessment, Linear Analog Self-Assessment, and Was It Worth It questionnaire]. Pharmacokinetic and pharmacogenetic studies were added to determine if there are age-specific alterations in drug metabolism beyond the decline of basic organ function in older adults. A teleconference was held between NCCTG, CALGB and the NCI Division of Cancer Prevention representatives supporting the addition of two frailty assessments (Rockwood Canadian Study of Health and Aging Clinical Frailty Scale and NCCTG Brief Frailty Inventory), and another QoL assessment (EQ-5D).

2.4. Process of Trial Development

N0949 developed as a result of input from all relevant stakeholders. Starting in 2009, investigators from NCCTG (Grothey) and CALGB (McCleary) proposed a study to understand the additive toxicity and survival benefit of oxaliplatin in the setting of mCRC. The trial was investigator driven with input from NCCTG and the Gastrointestinal and Cancer in Elderly committees of the CALGB, active patient advocates, community oncologists and academic center leaders. Patient advocates raised concern regarding use of age as a selection factor and questioned whether the results of the trial would allow insurance payers to deny oxaliplatin to older adults. However, patient advocates were in favor of understanding factors associated with the best treatment outcomes for older adults, acknowledging that performance status alone does not adequately predict outcome. Community oncologists sought clarity on dosing and confirming provider preference for fluoropyrimidine use in the control arm. Both oncologists and patients raised concern regarding potential toxicity of oxaliplatin in older adults, somewhat reassured by the planned correlative studies to measure neurotoxicity, frailty, and quality of life directly from the patient. The proposal was revised to address these valid concerns, then submitted for approvals by the NCCTG, CALGB and National Cancer Institution (NCI).

2.5. Revised Trial Design

In May 2010, the Gastrointestinal Steering Committee (GISC) of the Cancer Therapy Evaluation Program (CTEP) of the NCI performed a consensus evaluation of the proposal, raising concerns about feasibility, statistical design and quality of life. We responded with appropriate changes in response to those concerns. Key changes to the protocol included [1] modifying the bevacizumab dose and treatment schedule in the capecitabine control arm and [2] discontinuing oxaliplatin after 8 mFOLFOX7 treatment cycles when a cumulative dose of 680 mg/m^2 oxaliplatin had been administered, [3] including patients age 70–74 to stimulate trial enrollment but limiting this subset to no greater than 25% of the cohort to make sure results were also generalizable to

Please cite this article as: McCleary NJ, et al, Challenges of conducting a prospective clinical trial for older patients: Lessons learned from NCCTG N0949 (alliance), J Geriatr Oncol (2017), http://dx.doi.org/10.1016/j.jgo.2017.08.005