Contemporary Clinical Trials Communications 9 (2018) 45–49

Contents lists available at ScienceDirect

Contemporary Clinical Trials Communications

journal homepage: www.elsevier.com/locate/conctc

Barriers to non-small cell lung cancer trial eligibility

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ARTICLE INFO

Keywords:
Lung cancer
Trials
Eligibility
Barriers

ABSTRACT

Introduction: Cancer clinical trial (CCT) enrollment is low potentially threatening the generalizability of trial results and expedited regulatory approvals. We assessed whether type of initial patient appointment for non-small cell lung cancer (NSCLC) is associated with CCT eligibility.

Methods: Using a patient-to-accrual framework, we conducted a quasi-retrospective cohort pilot study at Sidney Kimmel Comprehensive Cancer Center (SKCCC), Baltimore, Maryland. 153 NSCLC patients new to SKCCC were categorized based on type of initial appointment: patients diagnosed or treated and patients seen for a consultation. CCT eligibility was determined by comparing eligibility criteria for each open trial to the electronic medical record (EMR) of each patient at every office visit occurring within 6-months of initial visit.

Results: We found no association between type of initial appointment and CCT eligibility (OR, 1.15; 95% CI, 0.49–2.73). Analyses did suggest current smokers were less likely to be eligible for trials compared to never smokers (OR, 0.15; 95% CI, 0.03–0.64), and stage 4 patients with second line therapy or greater were more likely to be eligible than stage 1 or 2 patients (OR, 5.18; 95% CI, 1.08–24.75). Additional analyses suggested most current smokers and stage 1 or 2 patients had trials available but were still ineligible.

Conclusions: SKCCC has a diverse portfolio of trials available for NSCLC patients and should consider research strategies to re-examine eligibility criteria for future trials to ensure increased enrollment of current smokers and stage 1 or 2 patients. We could not confirm whether type of initial visit was related to eligibility.

1. Introduction

Cancer clinical trial (CCT) enrollment has been low for decades and is a central issue in oncology because the profile of trial participants does not match the diversity found in treatment populations. CCTs differentially exclude minorities, female, and older patients threatening the generalizability of trial results and expedited regulatory approvals [1,2].

Patient-, physician-, and protocol-centered factors are known to affect CCT enrollment [3]. A patient's willingness to enroll may depend on travel distance, treatment options, internet access, income, trust, and patient preferences [4–10]. Known physician-centered factors include incompatibility of protocols with normal practice, lack of compliance with protocols, consent procedures, discussion of trials, timing of trial information presentation, and time constraints [9,11,12]. Protocol-centered factors include limited trial availability and potentially overly restrictive eligibility criteria (e.g., prior cancer in early-stage or stage 4 lung cancer patients) [2,3,13–15].

Previous interventions to remove barriers to CCT enrollment have focused on physician- and patient-centered factors, like trial education and navigation systems [16–18]. In practice, intervention benefits have been limited suggesting protocol-centered or more comprehensive interventions should be considered [16–21]. For example, Ohio State University Comprehensive Cancer Center (OSUCCC) increased CCT enrollment 40% within two years by increasing oversight of the CCT process; educating stakeholders (e.g., patients, physicians, staff, leadership, etc.); ensuring CCTs are available irrespective of cancer type and stage of disease; and improving trial enrollment operations and infrastructure [20].

Building on the OSUCCC campaign, patient-to-accrual frameworks that address patient-, physician-, and protocol-centered factors have the potential to identify barriers and increase enrollment through subsequent interventions [20,22]. According to one established framework, there are seven steps to enrollment [1]: trials must be available for a patient's cancer type, stage, and line of therapy [2], patient must be eligible for the trial(s) [3], physician must not triage the patient [4], physician must discuss the trial with the patient [5], patient must be interested [6], patient must sign a consent form, and [7] patient must

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https://doi.org/10.1016/j.conctc.2017.11.010
Received 29 June 2017; Received in revised form 19 November 2017; Accepted 22 November 2017
Available online 24 November 2017

pass the final screen and enroll in the trial. Each step is conditional on the previous step [22]. Therefore trial availability and eligibility are upstream steps and potential barriers to enrollment that would require institution- or protocol-specific interventions.

Lung cancer is the number one cause of cancer-related death in the U.S. making it a research priority across the country, and, like other CCTs, enrollment is low [1,23]. Given that National Cancer Institute (NCI) sponsored CCTs are listed online to help cancer patients determine their eligibility prior to seeking care, our primary goal was to assess whether type of initial appointment was related to CCT eligibility among a sample of non-small cell lung cancer (NSCLC) patients seen at Sidney Kimmel Comprehensive Cancer Center (SKCCC) [24,25]. We hypothesized consult patients would have higher odds of eligibility compared to patients seen for a diagnosis or treatment because savvy patients may self-navigate to trials they believe they are eligible for [26]. Secondary goals included assessing whether type of initial appointment or other factors were related to trial availability or eligibility conditional upon an available trial.

2. Materials and methods

2.1. Study design

A quasi-retrospective cohort design was used to investigate whether the type of initial appointment was related to trial eligibility at SKCCC. We examined each patient's electronic medical record (EMR) longitudinally for six months to determine trial availability and eligibility for each trial at every appointment. The date that eligibility screenings occurred in clinic was not recorded due to an assumption that each appointment was an opportunity to screen patients for eligibility.

The Johns Hopkins School of Medicine Institutional Review Board approved this study.

2.2. Study population

NSCLC patients seen for their first appointment at a Baltimore-area NCI comprehensive cancer center from July 2012 through January 2013 were identified in the EMR as new patients (n = 153). Each patient was followed in the EMR until they became eligible for a trial or they were administratively censored 6 months after their initial visit.

2.3. Independent variables

The independent variable was type of initial appointment, which was dichotomized: those seeking diagnosis or treatment at the initial appointment and those seeking a consult but no diagnosis or treatment at the initial appointment. The Johns Hopkins Hospital cancer registry categorized each study patient.

Administrative staff at SKCCC recorded patients' smoking status (never, former, or current) and demographic data before the patients' initial visit. Patient demographics included: age at time of initial visit, sex (male or female), and race (white, black, or other races). It is presumed the patients self-reported their race. Each variable was abstracted from the EMR by one of the investigators (JH).

2.4. Outcomes

The primary outcome was clinical trial eligibility. Eligibility was determined by comparing eligibility criteria for each open trial with the EMR of each patient at each appointment until they were eligible for a trial or 6 months from their initial visit had passed.

Secondary outcomes were trial availability and trial eligibility conditional on trial availability. Both were ascertained using the seven-step framework for CCT enrollment [7]. More specifically, trial availability was determined by crosschecking each patient's NSCLC stage-and-line of therapy with a list of available trials at each appointment.

Table 1
Baseline characteristics of NSCLC patients new to SKCCC.

Characteristic	Diagnosis or treatment (n = 67)	Consult only (n = 86)	Total (n = 153)	P value
Age, y	26 (38.8)	30 (34.9)	56 (36.6)	0.48
< 60	21 (31.3)	35 (40.7)	56 (36.6)	
60–69	20 (29.9)	21 (24.4)	41 (26.8)	
> = 70				
Sex, %	32 (47.8)	44 (51.2)	76 (49.7)	0.68
Male	35 (52.2)	42 (48.9)	77 (50.3)	
Female				
Race	46 (68.7)	63 (73.3)	109 (71.2)	0.13
White	16 (23.9)	11 (12.8)	27 (17.6)	
Black	5 (7.5)	12 (14.0)	17 (11.1)	
Other				
Smoking status	16 (23.9)	24 (27.9)	40 (26.1)	0.05
Never	33 (49.3)	52 (60.5)	85 (55.6)	
Former	18 (26.9)	10 (11.6)	28 (18.3)	
Current				
Stage and line of	11 (16.4)	4 (4.7)	15 (9.8)	< 0.001
treatment	16 (23.9)	11 (12.8)	27 (17.6)	
Stage 1 or 2	30 (44.8)	25 (29.1)	55 (35.9)	
Stage 3	10 (14.9)	46 (53.5)	56 (36.6)	
Stage 4: first line therapy				
Stage 4: second line therapy or greater				
Eligibility	41 (61.2)	36 (41.9)	77 (50.3)	0.18
Ineligible	26 (38.8)	50 (58.1)	76 (49.7)	
Eligible				

Lists of available trials were provided for two time points (June 2012 and June 2013). Only patients with available trials were examined further for trial eligibility per the same abstraction protocol as the primary outcome.

2.5. Statistical analysis

One NSCLC patient new to SKCCC had missing demographic values and was dropped from the data set after substantial efforts to locate the missing values were unsuccessful. Dropping one patient was not expected to influence the results. One hundred fifty-three NSCLC patients were included in the analyses.

Before testing our primary hypothesis, we identified covariates and potential confounders. The literature suggested age, sex, and race were related to enrollment but was less conclusive regarding smoking status and cancer stage-and-line of therapy [1]. Thus smoking status and stage-and-line of therapy were considered two potential confounders. Chi-square analyses were conducted to help identify relationships between these variables and our main exposure, appointment type, and our primary outcome, eligibility (Tables 1 and 2, respectively).

To test our primary hypothesis we created a multiple logistic regression model using the backwards selection method. Three separate models derived from the backwards selection were also compared using Akaike information criterion (AIC). The final model included the independent variable and all covariates and confounders: type of initial appointment, age, sex, race, smoking status, and cancer stage-and-line of therapy. A scatterplot of residuals versus fitted values was used to check model fit. Given that SKCCC has a smaller catchment area for African Americans, we also evaluated whether race modified the association between appointment type and eligibility using a likelihood ratio test [4].

To further examine the upstream steps or barriers to enrollment, we tested the relationships between type of initial appointment and trial availability and eligibility conditional on trial availability using chi-square analyses. Associations between significant confounders and secondary outcomes were also analyzed by chi-square analyses.