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The Bottleneck Effect in Lung Cancer Clinical Trials

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Abstract

Clinical trials provide the most promising way to improve treatment outcomes in cancer. This study examined the rate at which eligible patients with lung cancer, at a National Cancer Institute-designated cancer center in the South, were offered a clinical trial and explored for reasons for ineligibility. We retrospectively reviewed 300 randomly selected lung cancer patients' medical records seen in 2010, to assess clinical trial offers to eligible patients, reasons for not offering an eligible patient a trial, demographic factors associated with eligibility, and reasons for refusal among those offered a trial. Of the 300 patient charts, seven were excluded for lack of confirmed lung cancer diagnosis. Forty-six of the remaining 293 (15.7 %) patients were eligible for a clinical trial. Forty-five of the 46 (97.8 %) were considered for a trial by their oncologist. Thirty-five of the 45 (77.8 %) were offered a trial: 15 agreed (42.9 % of those offered, 5.1 % of patients reviewed), 11 declined, and 9 were undecided at the end of the review window. Patients with poor Eastern Cooperative Oncology Group (ECOG) performance status levels and small cell (SC) diagnoses were significantly less likely to be eligible for a trial. Results suggest that oncologists at the cancer center are effectively presenting all eligible patients with the option of a clinical trial;

however, there is a need to increase the number of approved clinical trials for patients with SC or ECOG score greater than 2.

Keywords

Oncology; Clinical trials; Lung cancer; Physician

Introduction

Lung cancer is responsible for more deaths than any other cancer type in both men and women. The 5-year survival rate for all stages of lung cancer combined is less than 16 % [1]. This poor outlook reinforces the long established need for investigational studies to advance treatment options and improve health outcomes. Clinical trials have been identified as the primary means for discovering the most effective treatments and cures for cancer [2–4]. However, rates of enrollment are significantly lower than the rates of cancer burden experienced by the USA patient population. It has been estimated that as few as 3–5 % of newly diagnosed cancer patients participate in clinical trials [5]. These low accrual rates are also upheld at comprehensive cancer centers, often thought to have the infrastructure and patient volumes to support clinical research [6]. Low accrual rates to cancer clinical trials have a negative impact on patient outcomes, treatment advances, and drug discovery. Low accruals impede the development of novel therapeutics by prolonging the duration of trials, often leading to the early closure of many potentially beneficial trials [5, 7]. Although lung cancers comprise the highest percentage of the cancer burden in the USA, those diagnosed with the disease are underrepresented in clinical trials when compared to leukemia and colorectal cancer patients [8]. Thus, expanding our understanding on the barriers associated with accrual to cancer clinical trials, particularly from the institution and physician's perspective, is essential to making impact on this disease.

Multiple studies at single institutions have identified specific barriers to clinical trial enrollment, including patient- and administration-related factors such as lack of awareness about clinical trials [9] and availability of appropriate clinical trials [10], respectively. Others have focused on the patient–physician interaction during the decision-making process [5, 11]. Physicians play an important role; the majority of discussions about clinical trials are initiated by a patient's oncologist. Several studies suggest that a physician's decision not to offer a patient a trial is made prior to the evaluation of protocol eligibility, indicating that physician bias may come into play [5]. The failure of physicians to offer eligible patients a trial may be attributable to a number of obstacles faced, such as time constraints, perceived loss of control over treatment, and data management issues [11–14]. Research suggests that physicians play a major role in whether or not patients are enrolled in a clinical trial [7, 14, 15]. Patients often report that the most important factor in their decision to participate in a trial was the fact that their physician offered it to them [7]. Physicians may experience problems in initiating conversations about clinical trials with patients. Physician issues have been strongly linked to lack of accrual in phase I trials [16, 17]. Once a physician identifies a patient as an eligible clinical trial candidate and extends the offer to enroll, the patient has the choice to agree or refuse to participate. Common

reasons for refusal include lack of awareness; logistical barriers, such as insurance costs and travel; personal beliefs about safety; side effects and randomization; and perceived purpose of clinical trials [5–7, 18].

Fenton et al. sought to gain further insight into the barriers to clinical trial participation by assessing the perceptions of both patient and oncologists. Survey results indicate that there are discrepancies between patients' actual beliefs and the oncologists' view of patient beliefs [7]. Such discrepancies further complicate the issue of initial decisions of clinical trials as viable treatment options. Lara et al. utilized a retrospective design to evaluate physician and patient barriers to clinical trial accrual. They found that physicians cited the following reasons for not considering clinical trials: no available protocol, previous lines of therapy, no diagnosis, poor performance status, and patients not expected to return. Of those patients who were considered a candidate, only about 50 % had an available protocol for their disease characteristics [5]. These findings are consistent with other studies looking at accrual barriers.

Although lack of awareness and knowledge about clinical trials appears to affect all groups of cancer patients, lung cancer patients may be especially vulnerable to experiencing these barriers. Unlike patients with common cancers, lung cancer patients often feel that there is a stigma associated with their cancer, due to a public perception that all lung cancers are related to smoking [19]. As a result, lung cancer patients may be less likely to discuss issues regarding their diagnosis and treatment. Furthermore, the literature suggests that patients diagnosed with lung cancer are less likely to participate in clinical trials due to the uncertainty of the disease and the poor prognosis that accompanies delayed treatment [5]. This qualifies lung cancer patients as a subgroup of cancer patients that may need additional and tailored awareness and education about clinical trials.

The primary objective of this study was to retrospectively evaluate clinical trial offers among thoracic patients and to identify if specific patient or physician demographics impacted the offer of a clinical trial. The secondary objectives were to assess the reasons why a clinical trial was not offered to an eligible patient and to understand the reasons for refusal among eligible patients offered with a clinical trial. The overall goal was to better understand the physician, patient, and trial design barriers that may exist and to subsequently develop recommendations to address these issues within our institution.

Methods

Database

The subjects in this study were thoracic cancer patients seen by a thoracic oncologist at the National Cancer Institute (NCI)-designated cancer center in the South. A random sample of medical record numbers of 300 patients was generated by the Clinical Data Systems Administrator (IT department). All patient types were considered, including "new patients" defined as those who presented for their first appointment at the cancer Center, "newly established patients" defined as those who had been seen previously in another clinic at the cancer center but presented for their first appointment in the thoracic clinic, and "established patients" defined as those who had been seen for a minimum of one visit in the thoracic

clinic. The University of South Florida Institutional Review Board granted approval for this study.

Design and Setting

We conducted a retrospective medical record review of 300 patients who presented for an appointment with the Moffitt Cancer Center's thoracic oncologist between 1 August 2010 and 31 October 2010. The review window was selected to be a structurally representative of the department (i.e., consistent patient volume and full staffing). Before the study was conducted, four thoracic clinical trial coordinators summarized the inclusion and exclusion criteria for the 13 available treatment trials that were active during the time period of the data abstraction. Three research assistants were trained to cross-reference the patient medical records with the clinical trial criteria to determine patient eligibility. An inter-rater reliability rate of 95 % was obtained among the research assistants before their training was complete.

The research assistants were each assigned a set of medical record numbers to review. The medical records were reviewed using the Soarian, the institutions' electronic patient database. Abstractors reviewed all records of patient encounters within the 3-month window, focusing on visits in which treatment decisions would have occurred. Data were entered record by record, into a scannable data abstraction form, created by the center's Survey Methods Core. The study variables included patient status, attending physician, day of appointment, payor status, patient age range (<50, 51–70, and >71), gender, race/ethnicity, marital status, distance traveled to cancer center, lung cancer type, lung cancer stage, Eastern Cooperative Oncology Group (ECOG) performance status [0–4], patient eligibility for an available protocol, consideration and/or offer of a clinical trial, and acceptance or decline of a clinical trial. We recorded the number of patients who were (1) eligible for a clinical trial; (2) eligible and considered for a clinical trial; (3) eligible, considered, and offered a clinical trial; and (4) eligible, considered, offered, and accepted a clinical trial. For the purpose of this study, “considered” meant that the oncologist noted the possibility of clinical trial candidacy in the medical records. The “offered” designation meant that the oncologist directly offered clinical trial participation to the patient during the appointment, as listed in the medical record. Patients may have been considered but not offered a clinical trial if the patient met all eligibility criteria but nonmedical factors interfered. For example, if a physician considered a patient for a clinical trial but the patient did not return for the follow-up appointment, the patient would be listed as “considered but not offered.” If an eligible patient was not considered for a clinical trial, the reason was recorded. If a patient was offered a clinical trial but refused to participate, the reason for refusal was also recorded. In addition, the data abstraction form included a text box to enable the abstractors the opportunity to summarize reasons for ineligibility. The text was later hand coded, and emerging themes were recorded.

Statistical Analysis

Descriptive statistics were summarized, and Tables 1 and 2 list all study variables. Key values were the percentage of eligible patients offered a trial and the percentage of patients who accepted an offered trial. Variations in offer of trials to eligible patients were evaluated

with two-sided statistical tests and declared significant at an overall 5 % level. Prior to any of these tests, the variables were examined and combined into fewer categories to minimize low frequencies for a given category.

Results

A total of 300 medical records were reviewed and assessed. The final analysis included 293 medical records because seven patients did not have a confirmed primary lung cancer diagnosis. Table 1 shows the demographic characteristics of the sample. Patient age ranged between 51 and 70 years; of the patients, 51 % were female, 92 % were White non-Hispanic, 67 % were married, 68 % were classified as established patients in the thoracic clinic, 95 % were insured, and 48 % lived within 50 miles of the institution. Our study population was a representative of the typical patient population in the thoracic clinic. There were no statistically significant differences when comparing men and women.

The cancer-related measures for all study participants are presented in Table 2. About half of the patients presented with a ECOG performance status of 1, 83 % of the patients were diagnosed with non-small cell lung cancer (NSCLC), and 8 % of patients were diagnosed with small cell lung cancer (SCLC). The most common type of NSCLC was adenocarcinoma, followed by squamous cell carcinoma. Almost 50 % of patients diagnosed with NSCLC presented with stage IV disease. The most common type of SCLC was at an extensive stage. It should be noted that during the review window, there were no available clinical trials for patients diagnosed with mesothelioma or limited-stage SCLC.

Table 2 also presents cancer-related measures by eligibility status. Forty-six of the 293 participants (15.7 %) were deemed eligible for a clinical trial during the review window. A higher percentage of eligible patients versus those not eligible (1) had a performance status of 0 or 1 ($P=0.005$), (2) had a NSCLC stage IV disease ($P=0.019$), and (3) had an extensive-stage SCLC ($P=0.034$). The most common reasons for patient ineligibility were poor ECOG performance status levels and select types of cancer diagnoses that were not associated with any available clinical trials.

As shown in Table 3, oncologists considered 45 (97.8 %) of the 46 eligible patients for an available clinical trial. The oncologists offered clinical trial participation to 35 of the 45 (77.8 %) considered patients. During the review window, 15 of those offered agreed to participate (33.3 % of those offered; 5.1 % of study participants), 11 patients declined to participate (24.4 % of those offered), and 9 patients were undecided (20.0 % of those offered a trial). The most common reason patients declined to participate was the long distance between their home and the cancer center.

Discussion

Our study aimed to assess clinical trial offers and outcomes in lung cancer patients. Results indicate that thoracic oncologists were efficient in considering and offering clinical trial participation to the majority of eligible patients. However, only 15 of 293 (5.1 %) of the eligible patients were eventually enrolled in a clinical trial. This figure is close to the national average but lower than that recommended by the NCI. The number of minority

patients included in the study was a representative of those seen in the thoracic clinic but significantly lower than their representation in the USA. The overwhelming majority of the study population was White non-Hispanic; less than 8 % of our sample was African-American, Hispanic, or Asian. The unique barriers faced by these underrepresented populations are frequently documented in the literature [20–22]. The Moffitt Cancer Center is actively developing new initiatives to increase its minority patient population and their subsequent representation in clinical trial studies.

Protocol eligibility criteria represent a major barrier to enrolling lung cancer patients. We found that many patients were excluded from any clinical trial consideration because of poor performance status. Clinical trials are typically designed for individuals who are ambulatory and capable of self-care. Participants must be moderately healthy so that investigators can concentrate on the effects of the investigational drug without significant ambiguity from the disease condition. Although this strategy is practical, it prohibits the sickest individuals from receiving the state-of-the-art cancer care provided in clinical trials. Lung cancer is a disease that carries heavy burden. Many patients are more willing to participate in clinical trials as the last resort when their treatment options are limited. It can be argued that separate trials should be made available to these individuals so that they too can benefit from and contribute to advances in clinical research.

Of the patients who were healthy enough to participate in a clinical trial, many were ineligible to participate because of their cancer type or stage. The unavailability of clinical trials for these patients represents a significant barrier. For patients diagnosed with mesothelioma or limited-stage SCLC, there were no available clinical trials during the review window. These patients were automatically excluded from clinical trial participation at the start of the appointment. In addition, there were significantly fewer trials available for patients with stages I–III NSCLC as compared to stage IV NSCLC. As with all types of cancer, lung cancer prognosis is better when the disease is detected and treated earlier. Thus, perhaps more clinical trials should be designed for early-stage patients, including adjuvant trials, to improve chances of cure in these patients.

This study outlines the methodology we used to assess clinical trial offers in our cancer center. Retrospective data abstraction and chart review are important methods for gaining better understanding on the practices and potential barriers that hinder accrual rates. This study has provided an insight into our patient population, helped to establish an accrual baseline, and enabled us to develop recommendations for future trial development. We recognize that retrospective chart analysis studies have limitations. Data abstractors utilizing physician-dictated clinic notes may not have a comprehensive depiction of the complexities that exist in patient assessment, physician–patient communication, and the decision-making process.

We believe that other institutions can use this process to monitor their clinical trial enrollment procedures and maintain quality assurance. Although we did not find significant lapses in a clinical trial offer at our cancer center, this may be dissimilar at other institutions. Furthermore, our study suggests the need for more detailed record-keeping procedures with respect to clinical trial consideration during appointments. Our goal would be to implement

a “clinical trial” section in each patient’s medical note where the oncologist would indicate whether or not available clinical trials were considered and discussed as an option. Another option may be to design a software program that cross-references information in the medical records with inclusion/exclusion criteria for available trials. This would ensure that all eligible patients are considered for participation and able to contribute to clinical research. The present work illustrates that diverse and improved strategies may be needed to address the continued issue of low clinical trial accrual, including addressing the role of physician communication.

There is a great need to develop a larger variety of lung cancer clinical trials since majority is designed for advanced stage disease. Recognizing the recurrence rates for those with early-stage disease, trials designed in the adjuvant setting and for early-stage disease may be important. In addition, inclusion and exclusion eligibility criteria should take into account that the majority of lung cancer patients have comorbidities, are older, and often have poorer performance status. Having better understanding on all the logistical and patient–physician barriers to clinical trial accrual has the potential to lead to both interventions and new ways of trial development, subsequently leading to therapeutic advances.

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Table 1

Descriptive statistics for patient characteristics

	All (N=293) n (%)	Men (N=144) n (%)	Women (N=149) n (%)
Demographic variables			
Age			
50 years	25 (8.5)	13 (9.0)	12 (8.1)
51–70 years	181 (61.8)	85 (59.0)	96 (64.4)
71 years	87 (29.7)	46 (31.9)	41 (27.5)
Race/ethnicity			
American Indian/Eskimo	0 (0.0)	0 (0.0)	0 (0.0)
Asian	6 (2.0)	2 (1.4)	4 (2.7)
Black or African-American	11 (3.8)	5 (3.5)	6 (4.0)
White	268 (91.5)	135 (93.8)	133 (89.3)
Hispanic	4 (1.4)	1 (0.7)	3 (2.0)
Unknown	4 (1.4)	1 (0.7)	3 (2.0)
Marital status			
Single	16 (5.5)	5 (3.5)	11 (7.4)
Married	196 (66.9)	115 (79.9)	81 (54.4)
Widowed	28 (9.6)	4 (2.8)	24 (16.1)
Divorced	40 (13.7)	13 (9.0)	27 (18.1)
Unknown	13 (4.4)	7 (4.9)	6 (4.0)
Appointment variables			
Patient status			
New	88 (30.0)	43 (29.9)	45 (30.2)
New established	6 (2.0)	3 (2.1)	3 (2.0)
Established	199 (67.9)	98 (68.1)	101 (67.8)
Appointment day of the week			
Monday	54 (18.4)	27 (18.8)	27 (18.1)
Tuesday	87 (29.7)	41 (28.5)	46 (30.9)
Wednesday	13 (4.4)	8 (5.6)	5 (3.4)
Thursday	76 (25.9)	37 (25.7)	39 (26.2)
Friday	62 (21.2)	31 (21.5)	31 (20.8)
Payor status			
Insurance	277 (94.5)	134 (93.1)	143 (96.0)
Self	10 (3.4)	6 (4.2)	4 (2.7)
Charity	6 (2.0)	4 (2.8)	2 (1.3)
Distance traveled			
50 miles	140 (47.8)	68 (47.2)	72 (48.3)
51–100 miles	84 (28.7)	42 (29.2)	42 (28.2)
101 miles	69 (23.5)	34 (23.6)	35 (23.5)

Table 2

Cancer-related measures by eligibility status

Variable	All (<i>n</i> (%)) <i>N</i> =293	Eligible (<i>n</i> (%)) <i>N</i> =46	Not eligible (<i>n</i> (%)) <i>N</i> =247
Cancer recurrence	42 (14.3)	9 (19.6)	33 (13.4)
Previous CT participation	41 (14.0)	3 (6.5)	38 (15.4)
Performance status			
0	83 (28.3)	9 (19.6)	74 (30.0)
1	147 (50.2)	33 (71.7)	114 (46.2)
2	52 (17.7)	4 (8.7)	48 (19.4)
3	10 (3.4)	0 (0.0)	10 (4.0)
4	1 (0.3)	0 (0.0)	0 (0.0)
Lung cancer diagnosis			
NSCLC	244 (83.3)	42 (91.3)	202 (81.8)
SCLC	22 (7.5)	4 (8.7)	18 (7.3)
Mesothelioma	10 (3.4)	0 (0.0)	10 (4.0)
Other	9 (3.1)	0 (0.0)	9 (3.6)
No diagnosis	8 (2.7)	0 (0.0)	8 (3.2)
NSCLC type	<i>N</i> =244	<i>N</i> =42	<i>N</i> =202
Adenocarcinoma	160 (65.6)	28 (66.7)	132 (65.3)
Squamous cell	65 (26.6)	13 (31.0)	52 (25.7)
Large cell	2 (0.8)	0 (0.0)	2 (1.0)
NOS	13 (5.3)	1 (2.4)	12 (5.9)
Other	4 (1.6)	0 (0.0)	4 (2.0)
NSCLC stage			
0	1 (0.4)	0 (0.0)	1 (0.5)
I	29 (11.9)	3 (7.1)	26 (12.9)
II	22 (9.0)	2 (4.8)	20 (9.9)
III	64 (26.2)	7 (16.7)	57 (28.2)
IV	120 (49.2)	27 (64.3)	93 (46.0)
Unstaged	7 (2.9)	3 (7.1)	4 (2.0)
Missing data (<i>n</i> =1)	1 (0.4)	0 (0.0)	1 (0.5)
SCLC stage	<i>N</i> =22	<i>N</i> =4	<i>N</i> =18
Limited	7 (31.8)	0 (0.0)	7 (38.9)
Extensive	13 (59.1)	4 (100)	9 (50.0)
Unstaged	2 (9.1)	0 (0.0)	2 (11.1)

Table 3

Clinical trial outcomes

Category	No.
1 Eligible for a clinical trial	46 of 293
2 Eligible and considered for a clinical trial	45 of 46
Eligible but not considered for a clinical trial	1 of 46
3 Eligible, considered, and offered a clinical trial	35 of 45
Eligible and considered but not offered a clinical trial	10 of 45
4 Eligible, considered, offered, and accepted a clinical trial	15 of 35