Barriers to Enrollment in Non-small Cell Lung Cancer Therapeutic Clinical Trials

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Introduction: Despite recent advances in treatment, lung cancer remains the leading cause of cancer-related mortality in the United States. Therefore, there is a strong need for developing clinical trials in lung cancer therapeutics. Only a small fraction of patients with lung cancer are enrolled in clinical trials. It is critical to understand the barriers to participation in lung cancer clinical trials.

Methods: We reviewed the outpatient charts of consecutive patients with non-small cell lung cancer who presented for initial evaluation or consultation for further therapeutic management to the thoracic medical oncology group at the Alvin J. Siteman Cancer Center between January 1, 2006, and December 31, 2006. Available and appropriate clinical trials specific to the histologic subtype and stage were presented to the patients routinely, and reasons for nonenrollment were documented. We collected information on age, gender, ethnicity, histology, stage, performance status (PS), and insurance status.

Results: During the study period, 263 patients with non-small cell lung cancer were identified for the study. After initial screening, 183 patients had clinical trials available, which were appropriate for their diagnosis and stage of disease. One hundred one patients (55.2%) were ineligible for enrollment in a clinical trial. The most common reasons for ineligibility were poor PS (18%), need for emergent radiation (12%), lack of adequate staging information (6%), and comorbid conditions (4.9%). Despite being eligible for participation, 57 patients (31.1%) did not enroll in a clinical trial. Patient refusal accounted for 8.7%. The problems with transportation and distance from the medical center were reasons given for nonparticipation by 7.1%. Eleven patients (6%) did not participate in a clinical trial because of insurance issues. Ultimately, 25 patients (13.7%) were enrolled in a clinical trial.

Conclusions: Poor PS, the need for emergent radiation, and patient refusal were the most common reasons for not participating in a clinical trial.

Key Words: Lung cancer, Clinical trial, Patients, Accrual, Barriers.

The American Cancer Society estimates 159,390 lung cancer-related deaths in 2009.¹ Non-small cell lung cancer (NSCLC) accounts for approximately 87% of lung cancer cases.² Approximately 70% of patients diagnosed with lung cancer have stage III or IV disease at the time of presentation.³ With the introduction of novel agents for systemic therapy, we have seen a modest improvement in overall survival of patients with NSCLC.⁴ Adult patients with cancer are seldom enrolled in clinical trials.⁵⁻⁷ Accrual rates for cancer clinical trials are low even in established comprehensive cancer centers in the United States. Identifying factors limiting enrollment in lung cancer therapeutic clinical trials is crucial in designing trials geared to focus on problem areas. Therefore, we performed this study to specifically evaluate the barriers to enrollment in NSCLC clinical trials in a tertiary care center.

MATERIALS AND METHODS

We reviewed the charts of consecutive outpatients with NSCLC who presented for initial evaluation or consultation for further therapeutic management to the thoracic medical oncology group at the Alvin J. Siteman Cancer Center (SCC) between January 1, 2006, and December 31, 2006.

The SCC is a National Cancer Institute-designated Comprehensive Cancer Center at Washington University School of Medicine in St. Louis, Missouri. SCC is a member of the Cancer and Leukemia Group B (CALGB), Radiation Treatment Oncology Group, and American College of Surgical Oncology. SCC has two satellite locations in the community. The SCC thoracic medical oncology group consists of five medical oncologists and their staff. As a part of the thoracic oncology service, there are five thoracic surgeons and two radiation oncologists. The SCC clinical trial office...
has a large staff, with one regulatory manager and three research associates solely dedicated to the thoracic group.

Available and appropriate clinical trials are presented to the patients routinely, and reasons for nonenrollment are documented. We collected information on histology, stage, PS, and comorbid conditions. Appropriate studies at the time of initial consultation were noted from the SCC database based on the histologic subtype and staging before a formal individualized eligibility review was conducted.

The data analysis for this study was descriptive in nature. The distribution for continuous variables such as age was described using medians and ranges, whereas the categorical features were summarized with counts and frequencies. The patient characteristics across groups by enrollment status were compared using Kruskall-Wallis rank sum test or Fisher’s exact test as appropriate.

RESULTS

During the study period, 263 patients with NSCLC were seen for initial consultation by the thoracic medical oncology group at the SCC. During the time frame of this study, there were 29 therapeutic clinical trials open, which included 4 phase I/II trials, 22 phase II trials, and 3 phase III trials. Ten patients did not require treatment, and 26 patients had already initiated therapy and were not considered for participation in a therapeutic clinical trial in lung cancer. In addition, 44 patients did not have an appropriate clinical trial at the time of consultation. After initial screening, 183 patients had clinical trials available, which were appropriate for their histologic diagnosis and stage of disease before performing a comprehensive eligibility check. Figure 1 illustrates the process by which we identified these 183 patients. Table 1 shows the clinical characteristics of the 183 patients (94 men, 51.4%) with clinical trials available appropriate for their diagnosis and stage of disease. The median age of the group was 63 years (range 18–100 years). Consistent with local demographics, majority of patients were whites (70.5%) followed by African Americans (21.9%). The most common histologic subtype seen was adenocarcinoma (43.7%), followed by NSCLC-not otherwise specified (40.4%), squamous cell (13.1%), bronchioloalveolar (1.1%), large cell (0.5%), and other subtypes (1.1%). Most of the patients seen had stage IV (64.5%) or stage III (27.3%) disease. The majority of our patients carried private insurance (60.7%), whereas others had Medicare (18.6%), Medicaid (14.2%), or no insurance (6.6%).

Of the 183 patients for whom appropriate clinical trials were available (based on the histologic diagnosis and staging), 101 patients (55.2%) did not meet clinical trial eligibility when individualized review was conducted. Despite being eligible for trials, 57 patients (31.1%) were not enrolled in a clinical trial. Only 25 patients (13.7%) were ultimately enrolled in therapeutic clinical trials. Three patients enrolled in phase I/II trials, and the remaining 22 enrolled in phase III trials.

The reasons for not participating in a lung cancer therapeutic clinical trial are listed in Table 2. For consistency, we used 183 as the denominator for all calculated percentages in this table. As mentioned earlier, ineligibility for clinical trial participation was a major barrier. Reasons for ineligibility included poor PS (18%), need for emergent radiation (12%), lack of adequate staging information (6%), comorbid conditions (4.9%), presence of brain metastases (3.8%), second malignancy (3.3%), heavily pretreated patients (2.2%), contraindication to study drug (1.6%), mixed histology (1.1%), absence of measurable disease (1.1%), and other (1.1%). The last category included a patient with elevated liver enzymes and creatinine and another patient with too large radiation field to go on study.

Despite being eligible for participation, 57 patients did not enroll in a clinical trial. Patient refusal (no specific explanation provided) accounted for 8.7%. The problems with transportation and the distance from the medical center were given as reasons for nonparticipation by 7.1%. Eleven patients (6%) did not participate in a clinical trial because of insurance issues. Three patients (1.6%) were lost to follow-up, two patients (1.1%) had issues with compliance to therapy, and data were not available for two patients (1.1%).
Table 3 compares the characteristics of the following three groups: those who enrolled in a trial, patients who were eligible for trial participation but did not enroll in a trial, and patients who did not meet eligibility criteria for participation in a clinical trial although a trial was available for their histologic diagnosis and stage of disease. We did not find any significant differences in the any categories examined including gender, age, ethnicity, histology, stage, or insurance status perhaps likely to the small sample size.

**DISCUSSION**

Poor enrollment in clinical trials continues to be vexing problem in oncology today. The enrollment rate of 13.7% reported here is similar to what has been reported in the literature. Careful analyses of the factors limiting enrollment in clinical trials are necessary to make significant progress in the treatment of cancer. Even though trials are often available for patient with almost any stage of NSCLC, several factors influence eventual enrollment. Poor PS is a common problem in patients with NSCLC and is an adverse prognostic factor irrespective of stage. Most clinical trials are designed for patient with a PS of 0 to 1, even in the second-line setting. Clinical and translational studies need to be conducted with even more vigor in this population of patients with NSCLC.

Persistent and continuing low accrual rates hinder progress in this field by prolonging the duration of trials, leading to premature closure of studies from poor accrual and generating insufficient data to analyze. For instance, 9.4% of CALGB protocols failed to meet accrual goals over a 9-year period (1989–1997), and 20% of current CALGB protocols are lagging behind expected accruals. This poses considerable strain on as system already burdened with administrative issues as reported by Dilts and Sandler, who described half of the process steps required to open a trial to be nonvalue added steps. Clearly, the process of opening trials needs to be streamlined, and efforts need to be made to improve enrollment on clinical trials.

Lack of adequate reimbursement and infrastructure, time constraints, and their own misconception of patients’ attitudes about research could dampen physicians’ enthusiasm to promote participation in clinical trials. Fenton et al. analyzed data from a US national online survey conducted among 200 patients with lung cancer, 206 patients with other cancers, and 200 oncologists to compare their perception regarding clinical trials. Almost half of the oncologists surveyed reported that patients’ fear of side effects and being assigned to the placebo arm were two critical factors limiting participation in lung cancer clinical trials. However, when the authors surveyed a group of 200 patients with lung cancer,
only a minority reported fear of placebo (8%) or side effects (10%) as their major concerns.7

Reasons for patient refusal to participate in a clinical trial have been studied in patients with lung cancer. The most commonly cited ones are the difficulties associated with a randomized study design and the personal desire to be actively involved in decision making, and distrust of the medical profession with the refusal to see oneself as an experimental subject, insurance denial, and distance from clinic.5,12,13 Transportation was a barrier to clinical trial participation in our study. To assist patients traveling long distances for consultation, most large centers, including SCC, have free lodging arrangements for patients and their families. Although it may be possible for patients to make a single trip for second opinion regarding therapy or to be intermittently seen while being primarily managed by a local oncologist, repeated trips for the purpose of receiving investigational therapy or participating in a clinical trial may not be feasible. This supports the role of the Community Clinical Oncology Program in connecting large academic centers, which design and open clinical trials, to community physicians who accrue patients to these trials.

National Institutes of Health stipulates inclusion of minority groups in clinical trials.14 However, representation of racial and ethnic minorities in clinical trials has remained low.15,16 Bolen et al.14 constructed a framework for choosing a priori recruitment goals for underrepresented groups in an effort to increase their representation in clinical trials. However, it is possible that underrepresentation of minorities, such as African American patients in cancer clinical trials may be confounded by other variables, such as education and socioeconomic status, as Advani et al.17 found in a pilot study. Interventions that target community outreach, research, and education in this group may translate into improved recruitment in clinical trials. Program for the Elimination of Cancer Disparities was established in October 2003 to address one of the SCC’s top priorities: reducing cancer disparities in our community. Program for the Elimination of Cancer Disparities coordinates SCC activities that enhance underserved patients’ access to quality clinical care and research studies, including educational activities, cancer prevention, screening, treatment, palliative care, and family support.

Insurance issues were also a significant barrier to enrollment in clinical trial at our institution. There is a perception that patients enrolled in clinical trials incur additional costs compared with patients receiving standard of care therapy.18 This leads to private insurance plans frequently denying reimbursement for patient care as a part of a clinical trial. However, studies looking at incremental treatment costs for patients on cancer clinical trials have found modest cost differences of 0 to 10%.19 More work needs to be done with insurance companies to ensure that standard of care treatment is covered for patients enrolled in clinical trials. Study-associated costs could be further reduced by simplifying enrollment criteria and eliminating unnecessary repetitive testing before, during, and after treatment. Data collection can also be simplified, so that only data pertaining to serious adverse events are collected.

With the increasing availability of several agents for NSCLC, there is an urgent need to develop innovative strategies to improve clinical trial accrual. It is difficult to make meaningful progress in the treatment of NSCLC without overhauling the clinical trial process. This can only be achieved by developing appropriate clinical trials for specific subpopulations (clinically and molecularly defined), educating patients and physicians about the implications of research, and most importantly easing the cumbersome administrative burdens currently associated with clinical trials.

ACKNOWLEDGMENTS

The Alvin J. Siteman Cancer Center is supported by NCI Cancer Center support grant P30 CA91842.

REFERENCES


