ORIGINAL ARTICLE

Patients with Advanced Non–Small Cell Lung Cancer: Are Research Biopsies a Barrier to Participation in Clinical Trials?

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ABSTRACT

Objectives: Clinical trials of therapies for non–small cell lung cancer (NSCLC) are increasingly requiring mandatory tumor samples or research biopsies, both of which are potential barriers to trial participation. We assessed the impact of performance of research biopsies on the enrollment of patients with advanced NSCLC in clinical trials.

Methods: The cases of patients with advanced NSCLC who had been evaluated for clinical trials of systemic therapy at the Princess Margaret Cancer Centre from January 2007 to March 2015 were reviewed.

Results: Of the 55 clinical trials identified, 38 required tumor samples for enrollment. Six mandated repeat biopsies, whereas 32 permitted use of archival samples. Trial participation was offered to 636 patients at 940 unique study encounters, with some patients enrolling in multiple trials. Of the patients in 549 encounters during which participation in a therapeutic trial was offered, 60% received study treatment. More patients received study treatment (83% versus 55%, $p < 0.0001$) and study treatment was started earlier (after 9 days versus after 16, $p = 0.002$) when the trial did not have a mandatory tissue sample requirement. A similar trend was noted for trials permitting use of archival tissue versus mandatory repeat biopsies. The most common barriers to trial enrollment included absence of a required biomarker (34%), withdrawal of consent (20%), deterioration or death (17%), other exclusion criteria (15%), and insufficient biopsy tissue (10%).

Conclusion: A growing number of NSCLC trials are requiring tumor tissue for treatment eligibility, which appears to be a significant barrier to trial enrollment. Potential solutions include use of available diagnostic samples (e.g., cytology samples), development of peripheral blood assays for molecular markers, faster central laboratory testing turnaround time, and more resources for rapid biopsy.

Keywords: Non–small cell lung cancer; Clinical trial; Research biopsy; Barrier

Introduction

Lung cancer is the most common cancer worldwide and the leading cause of cancer deaths. An improved understanding of the molecular basis of non–small cell lung cancer (NSCLC), along with the development of molecularly targeted therapies, has led to major improvements in disease outcomes.[1] The effectiveness of agents targeting epidermal growth factor gene (*EGFR*)-mutant and anaplastic lymphoma kinase gene (*ALK*)-rearranged NSCLC has been well established, and molecular testing has become standard of care.[2–4] Further studies of next-generation targeted therapies for advanced NSCLC are ongoing.

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Most patients with NSCLC have advanced or unresectable disease when first seen and often are investigated by using procedures such as bronchoscopic biopsy or computed tomography–guided percutaneous needle biopsy.[5] Such diagnostic procedures yield small histologic or cytologic samples that often are adequate for diagnosis of malignancy; frequently, however, little or no tissue remains for additional diagnostic studies. For patients who have had metastatic disease for an extended period of time, diagnostic biopsy samples taken months or years previously may not accurately reflect the current molecular profile of the patient's disease.[6]

Many contemporary clinical trials of molecularly targeted therapy for NSCLC mandate performance of repeat research biopsies or submission of archival tumor tissue samples for analysis.[6] Although research biopsies may not result in direct personal benefit to the patient, they may be used for integral biomarker analysis to determine eligibility for a specific investigational therapy because treatment activity may be improved by molecular selection. Alternatively, research biopsies may be used for future exploration of predictive biomarkers to establish associations between molecular tumor features and clinical outcome. Such indications for tumor analysis apply to both repeat biopsies and analysis of archival tissue. The tension between exposing patients to the additional procedural risks of research biopsies for exploratory assays with unclear direct clinical benefit has led to ethical debate. Supporters argue that exploratory data obtained from research biopsies are critical to clarifying the mechanism of action of investigational agents and guiding treatment decisions for future patients.[7,8] Opponents argue that mandatory research biopsies expose patients to risk with no direct clinical or scientific benefit, particularly in the setting of early phase trials.[9,10] In addition, patients may perceive harm as a result of losing access to promising, even if unproven, experimental therapies if they are unable to undergo the research biopsies that are required for enrollment.[11]

Despite this ethical debate, many clinical trials of therapies for advanced NSCLC now require mandatory biopsies or archival tissue. In this study, we assess the impact of mandatory tissue sample or biopsy requirements on enrollment in clinical trials of therapies for advanced NSCLC.

Methods

Study design and population

We reviewed the cases of patients with advanced NSCLC who had been evaluated for clinical trials of systemic therapy at the Princess Margaret Cancer Centre, a major comprehensive cancer center with a focus on clinical trials, from January 2007 to March 2015. Study coordinators tracked patients who had been screened for trials prospectively. The institutional research ethics board reviewed and approved this study.

Patients screened for phase I, II, and III systemic therapy trials were included. Patients screened for research molecular profiling also were included. Those screened only for radiation oncology, surgical or supportive care trials, observational studies, and surveys were excluded.

Objectives

The primary objective was to determine the impact of mandatory tumor tissue requirements in clinical trials on the proportion of patients with advanced NSCLC who subsequently enrolled in those trials and proceeded to receive study therapy. A secondary objective was to determine the impact of mandatory tumor tissue requirements on the time from initial consent to when a repeat biopsy sample was obtained and study therapy was started. Finally, we evaluated the reasons why patients screened for clinical trials were unable to proceed to study enrollment.

Data collection

Trial characteristics, including phase and tumor tissue requirement, were determined by reviewing study protocols (by C.L. and M.S.). The prospective data collected (by N.N., A.F., N.P.L., D.Z., M.S., T.P., C.L., and M.S.) included patient demographics, trial outcomes (including reasons why patients were excluded from or did not enroll in trials), and detailed timeline information (including time of initial consent, repeat biopsy, and initiation of study treatment). These data were confirmed in clinical notes (by C.L. and M.S.).

Data analysis

Descriptive analysis was used to summarize trial and patient characteristics. Fisher's exact test, the Wilcoxon-Mann-Whitney test, and the Kruskal-Wallis test were performed where appropriate to test for differences among the groups. Statistical analysis was carried out using SAS v9.3 (Cary, NC).

Results

Trial characteristics

Overall, 55 trials were identified and included in this analysis (Fig. 1). All trials were linked to investigational therapy except for one molecular profiling study that was not linked directly to therapy. The 54 trials with investigational therapy included 12 phase I, six phase I/II, 18 phase II, one phase II/III, and 17 phase III trials. Thirty-eight trials (69%) required tumor tissue for