Expectations in the Care of Lung Cancer

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OVERVIEW

One of the main challenges oncologists face in the care of patients with lung cancer is the decision to incorporate new clinical trial data into routine clinical practice. Beyond the question of statistical significance, which is a more objective metric, are the results meaningful and applicable to a broader population? Furthermore, in an era of value care, do the results justify a potential increase in costs? This article discusses the main points that clinicians consider in their decision-making process and illustrates the arguments with real-life examples.

A daily challenge faced by all oncologists is how to apply the evidence from clinical trials to patients in the real world. Is a clinical trial deemed positive only on statistical or also on clinical grounds? Is the advance truly meaningful to patients, well tolerated, and affordable? Translating data into practice can be a challenge, particularly for clinical scenarios that fall outside the bounds of existing clinical practice guidelines.

In the first section of this article, we discuss trials in advanced non–small cell lung cancer (NSCLC), in which questions about statistical and clinical significance were debated among clinical experts and patient advocates. In the second section, we debate clinical trial endpoints and the applicability of results to clinical practice. In the third section, health care costs, clinical pathways, and value care are addressed.

STATISTICAL VERSUS CLINICAL SIGNIFICANCE

Definitions

When interpreting the results of a clinical trial, physicians interpret the outcomes under two different perspectives: the statistical significance and the clinical significance. The former is an objective, mathematical, and reproducible metric, whereas the latter is often undefined, largely subjective, and mostly left to the reader’s judgment. Both are subject to misinterpretation. Physicians often assume that low p values are a measure of the strength of the effect (not necessarily) or that clinical significance implies that the benefit of the intervention can be applied to the entire population at risk (not necessarily). Examples abound of clinical trials that are statistically significant but clinically irrelevant or, perhaps less common, trials that did not meet statistical significance yet had clinical applicability to certain patient subsets.

Statistical significance relates to how likely the observed effect is due to random chance rather than a true difference between the treatment arms. The smaller the p value, the less likely the results were obtained by chance or that the null hypothesis was true. On the other hand, there is no accepted definition of clinical significance. The closest concept is the minimally clinically important difference, which is the smallest treatment efficacy that leads to a change in a patient’s management. Others have attempted to define clinical significance by highlighting absolute risk reduction, as opposed to relative risk reduction, or the number needed to treat as a means to translate results of clinical trials into patient management. Quality-of-life issues and patient-reported outcomes also have been proposed as measures of clinical significance.

Chemotherapy

During the modern chemotherapy era, between the 1990s and early 2000s, when the median survival of patients with advanced NSCLC was approximately 8 months, clinical trials were designed to demonstrate a difference in median survival of approximately 2 months, arbitrarily set as a balance between a 1 month or less difference (considered not meaningful) and a 3 month or more improvement (considered very meaningful). Several of such trials, including several thousands of patients, were conducted but showed no significant differences among the various combination chemotherapy regimens. One trial, which compared cisplatin/docetaxel with cisplatin/vinorelbine, raised considerable debate in its interpretation and applicability to clinical practice. The difference in survival, in favor of cisplatin/docetaxel, was borderline statistically significant, but was not considered clinically significant by most clinicians. Although a commonly used combination, cisplatin/docetaxel did not gain widespread endorsement as the “regimen of choice” in advanced NSCLC.

More recently, the combination of cisplatin/pemetrexed was compared with cisplatin/gemcitabine, and a clear advantage emerged for the former in patients with nonsquamous histology. This study debunked an old paradigm as the first
to show a difference in outcome by histologic type in advanced disease. Likewise, the trials that tested the concept of maintenance have yielded solid benefits for patients and are considered both statistically and clinically significant.6

**Monoclonal Antibodies**

Two trials involving monoclonal antibodies illustrate the issues of statistical and clinical significance. The first showed that the addition of bevacizumab to chemotherapy improved survival, albeit at the cost of additional toxicity.7 Although a similar trial in Europe did not show an overall survival advantage (despite an improvement in progression-free survival [PFS]), bevacizumab has been adopted in the United States for eligible patients. From a clinician’s perspective, reluctance to add bevacizumab to chemotherapy is usually related to toxicity concerns and not so much the clinical significance of the trial. The cost-effectiveness implications are discussed below.

The second trial added cetuximab to chemotherapy in advanced NSCLC.8 Although the study met its primary endpoint of improvement in overall survival, cetuximab was not incorporated in first-line regimens, because the difference in median survival was not felt to be clinically meaningful despite multiple subsequent attempts to refine the target patient population.

More recently, ramucirumab was combined with docetaxel in the second-line treatment of NSCLC and led to a statistically significant improvement in survival compared with docetaxel alone.9 The magnitude of the difference in median survival was relatively small, but the results are unprecedented in the sense that no other agent, biologic or otherwise, has been shown to improve outcomes when added to a cytotoxic drug in the second-line treatment of NSCLC. It remains to be seen how these results will be interpreted by clinicians and adopted in clinical practice.

**Targeted Therapy**

The discovery that certain types of lung tumors harbor activating mutations that are sensitive to targeted agents has revolutionized the treatment of advanced NSCLC. Trials that compared a tyrosine kinase inhibitor (TKI) with chemotherapy as first-line therapy in patients with mutated tumors (either EGFR or ALK) confirmed the benefit of the TKI approach with respect to response rate and PFS.10 Overall survival, however, was not different, most likely because of crossover, which has led to some debate about the optimal timing and strategy of incorporating these agents in the treatment of NSCLC with sensitizing molecular alterations. In molecularly selected patients treated with the appropriate targeted agents, in comparison to standard therapies, differences in outcome tend to be robust, which illustrates that statistical significance does not always require a large number of patients when the expected treatment effect is meaningful.

**ASCO Meaningful Outcomes**

Members of the American Society of Clinical Oncology (ASCO) Clinical Research Committee were charged with proposing meaningful outcomes for clinical trials in several tumor types, including advanced NSCLC.11 The primary goal was to guide the design of clinical trials that would produce meaningful outcomes for patients. In NSCLC with a nonsquamous histology, the baseline for median survival was set at 13 months, and a meaningful incremental improvement was felt to be between 3.25 and 4 months. For squamous cell cancer, the baseline was 10 months and improvement of between 2.5 to 3 months was considered meaningful. Although these goals are aspirational and assume that biomarkers will be utilized in part for the selection of patients, it raises the bar and encourages investigators, sponsors, and patients to demand more of clinical trials.

**CLINICALLY MEANINGFUL TRIALS IN LUNG CANCER Studies of Real-World Effectiveness**

Given that clinical trials are conducted under highly controlled circumstances, it is reasonable to expect that trial results will not always be relevant or generalizable to one’s daily practice.

Several studies in lung cancer have suggested that the outcomes now seen in clinical trials may be reflected in the general lung cancer population, but patient selection remains important. After the establishment of adjuvant chemotherapy in early-stage NSCLC as a standard, Booth et al12 demonstrated that, although the uptake of adjuvant therapy in the target population only increased from 7% to 31%, the impact on survival was similar to the magnitude seen in clinical trials, with an increase in 4-year survival from 52.5% to 56.1% with the introduction of adjuvant therapy (p = 0.001).12 A recent Surveillance, Epidemiology, and End Results (SEER) analysis of the real-world effectiveness of novel agents in advanced NSCLC demonstrated that the use of platinum agents, second-line docetaxel, pemetrexed, and bevacizumab all were associated with a reduced risk of death.13 These data further support that positive results from clinical trials in advanced lung cancer do translate into benefits in clinical practice.

It is important to recall, however, that not all patients with a given diagnosis will receive the recommended treatment and
that multiple factors, including patient performance status, comorbidities, organ function, patient preference, and treatment access, all factor into treatment decisions. In a real-world analysis of Canadian patients with advanced NSCLC who were treated in a single-payer public health care system, 70% of patients were assessed by an oncologist at some point, but only 26% received systemic therapy. In those who received platinum doublet therapy and pemetrexed, outcomes were similar to or better than outcomes reported in clinical trials. However, older patients and those who had tumors with a squamous histology were significantly less likely to receive treatment for their disease. Similar data have been reported by Earle et al from U.S. SEER Medicare data, in which 23% of patients with advanced lung cancer received systemic therapy.

Thus, although oncologists are able to achieve excellent results in clinical practice, similar to those seen in trials, the achievement requires not only evidence-based practice but also careful patient selection and shared decision making.

**Special Populations**

Most clinical trials, from which practice guidelines are derived, include highly selected patients who have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1, few or no comorbidities, and a younger age. However, given that the median age of diagnosis in lung cancer is at least age 70 and that a majority of patients have an ECOG PS of 2 or greater, how useful are clinical trial results in the patients we actually see in practice? In a recent review of the inclusion of older adults in advanced lung cancer trials, a third of commonly cited trials specifically excluded older patients. Fortunately, there are multiple trials focused on the older patient population with lung cancer, but, again, not all patients in routine practice are suitable for the recommended therapy. Real-world analyses of older adults with lung cancer suggest that older patients do benefit from systemic therapy. Earle et al have examined the influence of age on systemic treatment for patients with advanced NSCLC in a real-world setting, using the SEER database. As age increased, the likelihood of receiving chemotherapy decreased, even though patients were still referred to medical oncologists for an opinion. Treatment rates varied inversely with the number of comorbidities.

In the case of potentially curative adjuvant chemotherapy, Cuffé et al demonstrated that, although older patients are prescribed adjuvant chemotherapy, the rate of uptake is approximately half of that seen in the entire population of patients with early-stage disease (16% vs. 31% overall). This population-based study confirmed that a survival benefit was seen in all age groups, and the tolerability of therapy in those patients older than age 70 selected to receive treatment appeared similar to that of younger patients.

The PS presents a similar challenge, because most patients with advanced lung cancer do not present with a PS of 0 or 1. Trials have shown that platinum-based doublet therapy is superior to single-agent treatment in patients who have a PS of 2, whereas guidelines recommend against treatment of patients who have a PS of 3. This decision is more challenging in practice, in which patients who have a PS of 2 are heterogeneous and there are additional factors for or against systemic therapy, including comorbidities, young age, prognostic factors, and potential delays in system access. Many databases have not routinely included PS assessment, but this is changing and will lead to more real-world data that will be available in addition to randomized trials to better inform best practices.

**Evolution in Trial Design**

The treatment of lung cancer has changed dramatically over the last decade. Lung cancer trials also have changed. In a recent analysis of phase III trials of systemic therapy of advanced NSCLC, there were significant shifts over a 30-year period. Although overall survival was a universal endpoint 30 years ago in these studies, there has been a perceptible increase in the use of PFS as an endpoint. This may be appropriate for studies of novel agents with major clinical benefits, which require crossover for ethical reasons. However, many trials that use PFS as the primary endpoint do not meet this criterion.

The number of agents under study in lung cancer is growing, as is the sample size of randomized, phase III trials—clear evidence of progress and hope in this disease. However, it appears that the magnitude of clinical benefit that investigators deem positive is falling. In the 1980s, a median survival increment of approximately 4 months in a phase III trial was considered positive, compared with 2.5 months in this last decade. The recommendations recently put forth by ASCO are described above. Though not specifically addressed, one could infer that benefit in trials for small cell carcinoma should approximate the benchmark set for squamous carcinoma. The document will not change existing trial plans nor drug approvals for lesser benefits, but it is hoped that this effort will encourage the oncology community and patients to be more demanding of the benefits gained from new therapies.

We have more agents approved in lung cancer than ever before, and decision making about treatment options has never been more complex. Patient outcomes recorded in a real-world setting, including survival and quality of life, and an open discussion about the value of therapy to the patient and society, has never been more important.

**Value in Lung Cancer Care: Use of Standardized Pathways**

Over the last several years, we have seen a rapid rise in the number of new agents to treat advanced NSCLC. Examples include new cytotoxic agents (e.g., nab-paclitaxel), targeted agents (e.g., erlotinib), biologic agents (e.g., bevacizumab), and, on the immediate horizon, immunomodulatory agents (e.g., nivolumab). Some of these new agents have led to only marginal advances; others have led to more impressive ones. All, however, have added substantial cost. This makes cost, as a part of decision making, more crucial today than ever before. In fact, oncologists are being asked to discuss the costs of treatment with patients, because cost of care is not simply a payer concern. Most patients bear some of the cost of their cancer care in the form of copays and coinsurance, and the prescribed treatment may be unaffordable. Patients should know what lies ahead for them.
because the harshest toxicity may be financial. High costs can be devastating to patients and their families, with up to 62% of all personal bankruptcies estimated to result from medical expenses.\textsuperscript{30}

This situation of similar outcomes among treatment regimens associated with high variations in cost sets the stage for clinical pathways. Simply put, can there be a succinct list of regimens that highlights the ones that provide the most value? And, if a pathway is implemented, can adherence to the pathway reduce costs compared with nonadherence while upholding or even improving quality and clinical outcomes? In 2005, US Oncology instituted a set of pathways, including a pathway for NSCLC. Pathway logic was embedded in the electronic medical record to ensure that pathways were visible at the point of care. The results of this program were first published in 2010.\textsuperscript{31} This was a retrospective study looking at two groups of patients with NSCLC over the course of an 18-month period: those who were treated entirely with on-pathway regimens and those who, at any time, were treated with an off-pathway regimen. (Because pathway adherence was not expected or meant to reach 100%, there was, indeed, a large group of patients who received at least one off-pathway regimen.) Results of the study showed a 35% reduction in outpatient costs with equivalent clinical outcomes (i.e., overall survival) for patients treated on pathway. Similar results have been shown by others. Feinberg\textsuperscript{32} reported on a payer-sponsored pathways program in which a large Mid-Atlantic payer collaborated with community oncologists in its provider network. Patients with breast, colon, or lung cancer who started chemotherapy after the initiation of the program were compared with baseline (historic) controls using the same claims database. Chemotherapy drug savings were $2,964 per patient for lung cancer.\textsuperscript{32}

The higher the cost of cancer treatment, the more the value is challenged. A simple equation to refer to is \textit{value = outcomes/cost}. If the difference in outcome is substantial between two treatments, good value may be upheld even if the superior treatment choice costs more. However, when two regimens are marginally different in outcome, higher costs quickly diminish value. Let’s look at one example: the addition of bevacizumab as a third agent in the treatment of advanced, untreated NSCLC. In the pivotal ECOG study, patients were assigned to either paclitaxel/carboplatin or paclitaxel/carboplatin with the addition of bevacizumab, and bevacizumab could be continued until disease progression occurred.\textsuperscript{7} The median survival times were 10.3 months and 12.3 months, respectively. Of note, there was a higher incidence of bleeding and treatment-related death in the bevacizumab-treated group. The costs of these regimens, using Medicare reimbursement (average sales price + 4.3%), were $625 for six cycles of paclitaxel/carboplatin and $74,000 for paclitaxel/carboplatin/bevacizumab with bevacizumab maintenance. Indeed, the results of this study were statistically significant, but were they clinically significant? Zhu et al\textsuperscript{33} reported on 4,168 Medicare beneficiaries older than age 65 who had advanced NSCLC and compared paclitaxel/carboplatin treatment with paclitaxel/carboplatin/bevacizumab.\textsuperscript{33} Median survival estimates were 8.9 and 9.5 months, respectively. The 1-year survival estimates were 39% for paclitaxel/carboplatin/bevacizumab and 40% for paclitaxel/carboplatin. The authors concluded that adding bevacizumab to carboplatin and paclitaxel chemotherapy was not associated with better survival among Medicare patients with advanced NSCLC. Chemotherapy does not represent the only cost center in cancer care; in fact, it is not even the costliest piece of the total-cost-of-care pie. In a Milliman report in which $49,000 was the average annual cancer-related cost for any cancer member, $21,000 was attributed to hospital costs and $13,800, to chemotherapy ($14,000 to other categories).\textsuperscript{34} Therefore, reducing preventable hospitalizations resulting from chemotherapy treatment is a worthwhile goal. Hoveman et al\textsuperscript{35} showed that, when a practice implements a formal clinical pathways program and also includes an outbound nurse call system, hospitalizations and total costs can be reduced. In a program sponsored by a payer in which clinical data and claims data were shared, patients with breast, colon, and lung cancer were enrolled in this care management program over a 2-year period.\textsuperscript{36} Compared with baseline (i.e., preprogram) practice data, there was a 48% overall reduction in emergency room visits, a 34% reduction in hospitalizations, and a 44% reduction in hospital days (i.e., length of stay). Greater adherence to clinical pathways was one of the factors contributing to these favorable results.

The simple goal of a clinical pathways initiative should be to drive value: to maintain or improve quality and control costs. To do this, pathways should be designed to favor cost-effective drugs and to challenge or exclude treatments that are of questionable clinical benefit, particularly when they are costly. This model has been shown to improve value in NSCLC. With the continued fast pace of new drugs entering the market for lung cancer, oncologists should take an active role in designing, initiating, updating, and adhering to pathways. If we do not, others will mandate it.

Disclosures of Potential Conflicts of Interest

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References


