Are We Making Progress in Lung Cancer Using Progression-Free Survival as a Surrogate End Point?

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Non-small-cell lung cancer (NSCLC) is the second most common cancer diagnosed in the United States and the leading cause of cancer-related mortality, with an estimated 221,200 new cases and 158,040 deaths anticipated in 2015. Despite advances in treatment, 5-year survival remains low at 16.8% across all patients, and only 2% in patients with stage 4 disease, indicating a need for novel therapies that affect survival. The identification of driver mutations in lung adenocarcinoma has dramatically changed the therapeutic landscape and improved treatment options for patients with advanced-stage disease, specifically, targeted options for patients with tumors that harbor mutations in the epidermal growth factor receptor (EGFR) gene or rearrangement in the anaplastic lymphoma kinase (ALK) gene. Whereas some targeted agents have been approved on the basis of data from randomized phase 3 trials, the ALK inhibitors crizotinib and ceritinib were granted preliminary approval by the Food and Drug Administration on the basis of early phase 1 data.2-3,4 Efficacy of crizotinib was later validated in randomized phase 3 trials.4,5

In this issue of JAMA Oncology, Lakdawalla and colleagues discuss the incremental social value of providing early access to new NSCLC treatment on the basis of progression-free survival (PFS) alone. Their analysis finds that early access based on any PFS benefit produces an overall loss of greater than $170,000 per newly treated patient per month, whereas granting access to drugs with PFS benefit between 1 and 3 months is more cost-effective. They also note that PFS benefit correlates with overall survival (OS) benefit in 71% of studies.

This analysis raises important questions regarding drug approval and treatment decision models in the context of inherently limited health care resources. Particularly with regard to NSCLC, the analysis further raises questions of how to evaluate cost-benefit in the era of targeted therapy.

In the Food and Drug Administration’s new drug approval process, cost considerations are taboo; approval is based strictly on a thorough assessment of whether the protocol-specified primary end point was met, and PFS is increasingly common as a primary end point. At the same time, ever-increasing costs of health care have long been the focus of nationwide attention and attempts at reform, begging the question, should such reform give greater weight to incremental social value of access to treatment? Furthermore, given net social value as a consideration, which parameters should be included in the value calculation? In the analysis presented by Lakdawalla and colleagues, indirect cost of treatment is considered, although not comprehensively; a more accurate picture may require a model with more detailed adjustment for net changes in overall treatment-related costs, such as differences in adverse events, need for additional clinic visits or hospitalizations due to therapy, and family member burden.

A more sophisticated model, to consider treatment crossover as well as more detailed consideration of indirect costs, may be particularly important in the era of targeted therapy, given that (i) when purchase price alone is considered, tar-
geted drug cost may well exceed that of chemotherapy, with a month of oral agent often costing in excess of $10,000; however, (2) targeted agents may not always confer OS benefit but may decrease incidence of grade 3 and 4 toxic effects, resulting in fewer health care visits, fewer hospitalizations, improved quality of life for the patient, and decreased family member burden. With the recent announcement of President Barack Obama’s precision medicine initiative, an even more rapid increase in the development of targeted therapies is likely, further underscoring the importance of probabilistic decision models for cancer treatment that take into account differences between chemotherapy and targeted therapy, or even among targeted agents with differing toxicity profiles.

For example, in the past 5 years, a multitude of clinical trials in select patient populations have demonstrated improved PFS when comparing targeted therapy to chemotherapy, without significant improvement in OS. In these patient populations, determination of OS benefit is complicated by the high number of patients who cross over to experimental therapy at the time of progression. Further contaminating survival data are the molecular heterogeneity of lung cancer, including different sensitivities to targeted therapies, as well as different mechanisms of acquired resistance; thus, repeated biopsy and resequencing of tumor tissue at progression may point to new therapeutic options for a given patient, introducing survival analysis complications similar to those caused by treatment crossover.

In short, correlation of PFS with OS may need to be reconsidered in patients receiving targeted agents; at the same time, such correlation may be less important in decision models for targeted therapy, due to increased value and decreased cost conferred even during PFS. In other words, minimum PFS benefit of 1 month, pointing to increased likelihood of OS benefit, may be necessary to justify the social cost for chemotherapy, while targeted drug development may benefit from a decision model that incorporates any superiority in PFS, with non-inferiority in OS.

As a final note, more rigorous quantitative models of net social value will require primary data from each individual participant in each study, to account for complications introduced by issues such as treatment crossover and/or new treatment options for acquired resistance. Although acquisition and analysis of raw data from many trials is difficult to achieve, such rigorous analysis may be indispensable when considering the incorporation of incremental social cost vs value into drug access decisions, especially given the sensitive and controversial nature of including cost as a factor in the drug approval process.

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REFERENCES