The Benefits of Achieving Stable Disease in Advanced Lung Cancer

Dr. Karen Kelly has written a timely discussion on the clinical benefit of achieving stable disease in advanced non-smallcell lung cancer (NSCLC). The goals of current therapy are to palliate symptoms, optimize quality of life (QOL), and prolong survival. It is argued that tumor shrinkage may not be mandatory to achieve these goals, particularly in the evaluation of molecular targeted therapies that may be cytostatic rather than cytotoxic in their mechanism of action. However, stable disease is not regarded as evidence of therapeutic efficacy by regulatory authorities. Furthermore, if based on radiologic measurements Continued on page 968. alone, this designation encompasses a heterogeneous population that includes patients who demonstrate unequivocal tumor shrinkage as well as many with tumor growth. Therefore, the case is presented to define stable disease in terms of clinical benefit by incorporating alternative trial end points such as symptom control, QOL, or biologic end points.

Should Stable Disease With Clinical Benefit Become an End Point in Advanced NSCLC Trials?

The TAX 317 trial and the Iressa Dose Evaluation in Advanced Lung Cancer (IDEAL)-1 and -2 trials provide the strongest evidence to date of the clinical benefit of stable disease. In the TAX 317 trial, docetaxel (Taxotere) as second-line therapy resulted in a median survival of 7.5 vs 4.6 months for best supportive care ($P = .01$), and a significant improvement in symptoms (pain and fatigue), despite an overall response rate of less than 10%. Thus, the proportion of patients who achieved stable disease (40%) must have contributed substantially to the clinical benefit and overall survival advantage observed in the entire group.[1] Similarly, in the IDEAL-1 and -2 trials, overall response rates were only 9% to 19%. However, stable disease was observed in 27% to 36%, and improvement in symptoms was demonstrated in approximately 40% of patients. These trials were not placebo-controlled, but symptoms improved in 71% of patients with stable disease compared to 17% of those with disease progression in IDEAL-2. Furthermore, although survival was not the primary outcome of either of the phase II IDEAL trials, a landmark analysis showed that the median survival of patients with stable disease in IDEAL-2 was 9.4 months vs 5.2 months for those with progression. The survival advantage was even more marked when patients with stable disease were analyzed according to improvement in symptoms: A median survival of 12.8 months was demonstrated for stable disease with symptom improvement vs 4.8 months for stable disease with no symptom improvement.[2] The question now is whether assessment of stable disease with clinical benefit should be designated as a major clinical end point in trials of NSCLC. The TAX 317 and IDEAL-1 and -2 trials suggest that this may be appropriate. However, the TAX 317 trial, although controlled with a notreatment arm, was relatively small with only 200 patients, and the IDEAL trials were neither placebo-controlled nor powered to assess survival. Before this question can be answered, it will be necessary to examine the results of large randomized trials to assess the true impact of achieving stable disease as a response to treatment. The 700-patient National Cancer Institute of Canada Clinical Trials Group study of erlotinib (Tarceva) in the second- and third-line setting (BR.21) had survival as its primary end point but undertook extensive evaluation of symptoms and QOL. The forthcoming data from this
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Conclusions
In conclusion, we concur with Dr. Kelly that stable disease may represent a positive therapeutic outcome in advanced NSCLC. However, further evidence from large randomized controlled trials is required, and consensus regarding the best instruments for measurement of symptoms and QOL is also warranted. At present, response rates, time to progression, and survival are still the preferred indicators of therapeutic efficacy in advanced NSCLC. Before stable disease with symptom benefit can be accepted as a new primary end point, it must be evaluated in the context of large randomized trials in which data on symptoms and QOL are, or have been, collected prospectively.

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