Can a Single Pill Replace Doublet Chemotherapy in First-Line Therapy of Advanced Non–Small Cell Lung Cancer?

□ □ Commentary on Giaccone et al., p. 6049

Paul A. Bunn, Jr.

Giaccone et al. are to be congratulated for conducting a trial of the oral agent erlotinib in previously untreated patients with non–small cell lung cancer (NSCLC; ref. 1). According to current American Society of Clinical Oncology guidelines, the standard therapy for these patients is a platinum doublet combination (although some nonplatinum doublets can be used when cisplatin or carboplatin is contraindicated; ref. 2). Standard platinum-based doublets produce objective response rates of 15% to 40% and median survivals of 8 to 10 months (2, 3). The small-molecule epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKI) were first studied in the second- and third-line setting in advanced NSCLC (4–6). Objective response rates in Western populations ranged from 8% to 20% with median survival times of 5.7 to 8.0 months, in Asia up to 27%. These response rates and survival times were similar to those reported for docetaxel and pemetrexed, the chemotherapeutic agents that are approved in the United States for second-line therapy of advanced NSCLC (7). These data raised the question of whether these oral TKIs could be equivalent and less toxic than platinum-based doublets in untreated patients. The trial design of Giaccone et al., however, is akin to comparing tamoxifen with standard chemotherapy in unselected breast cancer patients. The investigators recognized that biologically selected subsets of NSCLC patients were likely to have a better outcome than others when treated with EGFR TKIs. There were no validated selection criteria, however, at the time the study was designed.

In this study, the 53 eligible previously initiated patients with advanced NSCLC were treated with daily oral erlotinib (150 mg/d). The objective response rate was 23%, the median time to progression was 2.76 months, and the median survival was 12.85 months (1). There were no episodes of febrile neutropenia and no cases of death from toxicity. The efficacy data seem to be similar to published results from platinum-based doublets. For example, median objective response rates in the most recent Eastern Cooperative Oncology Group and the most recent Southwest Oncology Group and Cancer and Leukemia Group B trials with carboplatin/paclitaxel were 17%, 24%, and 30% (8–10). Median survivals in the paclitaxel/carboplatin arms in these trials were 8.1, 8.6, and 8.8 months, respectively. Clearly, the results in cooperative group, multi-institutional trials are usually inferior to those reported in single institutional trials likely because of less favorable patient characteristics. Nonetheless, this trial, conducted in three European centers, produced results similar to single-institution studies with platinum doublets. The patients entering this trial, however, had patient characteristics known to be associated with a favorable prognosis, such as female gender (23%) and never-smoking status (30%). These favorable characteristics are higher than in most U.S. randomized phase III trials.

The toxicity data in this study are superior to toxicity data reported for platinum-based doublet therapy. In the cooperative group trials described previously, the febrile neutropenia rates were 2% to 8% and grade 3 to 4 neutropenia rates were 55% to 63%, respectively (8–10). Therapy-related deaths were reported in each of these chemotherapy trials compared with no erlotinib therapy-related deaths described in this trial. There was only one grade 4 toxicity in erlotinib-treated patients. Are these data sufficient to conduct a randomized trial comparing erlotinib with platinum-based doublets in unselected patients or should such trials be conducted only in patients expressing some measure of EGFR?

The investigators approached the issue of patient selection by retrospective analysis of data from this trial. With regard to clinical features, they report that bronchioloalveolar carcinoma histology, never-smoking status, and age were significantly associated with positive outcome and that performance status was closely associated with survival outcome. These data are consistent with many other reports. Randomized studies indicated, however, that non-bronchioloalveolar carcinoma histology, smokers, and elderly patients may still benefit from EGFR TKI therapy (11, 12). The investigators concluded that there are no reliable clinical characteristics for patient selection.

What about biological characteristics? In this study, patients with K-ras mutations had a significantly worse survival compared with patients with wild-type K-ras (P = 0.006). Patients with mutations in the EGFR had longer survival than patients with wild-type receptor, although these differences were not significant. Increased EGFR gene copy number by chromogenic in situ hybridization did not predict for a favorable outcome, although only 13 cases were analyzed. The data for K-ras and EGFR mutations are similar to data published in several other reports, and it is interesting that patients with K-ras mutations seemed to have no benefit from EGFR TKI therapy (13, 14). The investigators concluded that the biological features that they studied were not sufficiently predictive for routine application.

Where do we go from here? It is clear from this report that some patients are likely to have benefit from EGFR TKIs that is equal to or superior to the benefit from standard
platinum-based doublet chemotherapy with less toxicity. But which patients? All studies reporting on EGFR copy number by fluorescence in situ hybridization, including the two large BR21 and ISEL randomized trials, showed that high EGFR copy number determined by fluorescence in situ hybridization is associated with high response rates and prolonged survival (14–17). EGFR copy number by quantitative PCR does not seem to predict survival (18). A recent American Society of Clinical Oncology report of a prospective trial with fluorescence in situ hybridization selection showed a response rate of 54%, a median time to progression of 6.5 months, and a median survival exceeding 12 months (19). Nearly all retrospective studies have reported higher response rates in patients with EGFR mutations. Some have reported improved survival in patients with EGFR mutations, whereas others have not (14–17). Recent prospective studies from Spain and Japan presented at American Society of Clinical Oncology in 2006 reported response rates of 90% and 81% and a median time to progression of >12 months in patients with EGFR mutations (20, 21). In early studies, EGFR cell surface protein levels by immunohistochemistry were not predictive of patient survival; however, several more recent phase II studies and the randomized BR21 and ISEL studies showed that positive immunohistochemical staining for EGFR may be associated with improved survival outcome after EGFR TKI therapy (15–17). Several retrospective studies found that K-ras mutations are associated with a low response rate and, some, a poor survival after EGFR TKI therapy but the fraction of patients with K-ras mutations are low.

The study of Giaccone et al. highlights the need for additional prospective studies of EGFR TKI therapy in biologically selected, previously untreated, NSCLC patients of all stages. Prospective randomized trials comparing these agents with chemotherapy in biologically selected patients have been designed based on fluorescence in situ hybridization, immunohistochemistry, and mutation analyses. Should these trials show superior outcomes, EGFR-positive lung cancer may be compared with estrogen receptor–positive breast cancer in which oral therapies are the standard initial therapy for metastatic disease.

References
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