Update on Epidermal Growth Factor Receptor Inhibitor Development in Lung Cancer

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Therapeutic strategies targeting the epidermal growth factor receptor (EGFR) are being evaluated in a number of ongoing clinical studies in non-small cell lung cancer (NSCLC). EGFR tyrosine kinase inhibitors (TKIs) are currently used worldwide to treat advanced refractory NSCLC, whereas the efficacy of anti-EGFR monoclonal antibodies remains to be established. Using molecular profiling to select patients to receive earlier EGFR targeted therapy as first-line treatment or in the adjuvant setting is an area of active research. Based on preclinical data, combining EGFR TKIs with other treatment modalities has promise, and clinical validation is underway. A new generation of irreversibly bound EGFR TKIs is being developed, and insights into the molecular biology of NSCLC should help to better define the patients who are most likely to benefit from these compounds. We summarize updates on EGFR targeted therapies that were presented during the sixth annual Targeted Therapies for the Treatment of Lung Cancer Conference in Los Angeles, CA; January 27–28, 2006.

Key Words: Non-small cell lung cancer, Epidermal growth factor receptor, Gefitinib, Erlotinib, Cetuximab, Panitumumab, Matuzumab.

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Molecular strategies to select patients for epidermal growth factor receptor tyrosine kinase inhibitor therapy

There are several clinical features of patients with non-small cell lung cancer (NSCLC) that are established predictors of response to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) therapy, including a never-smoking history, Asian race, female gender, and adenocarcinoma histology. However, data from the BR.21 study, a phase III randomized, placebo-controlled trial of salvage gefitinib, indicates that erlotinib yields a survival benefit even among patients without these features. Because clinical characteristics are insufficient to guide decision-making, a large international research effort is ongoing to identify biomarkers of response and survival benefit in patients treated with EGFR TKIs. EGFR protein expression, EGFR gene copy number, and EGFR tyrosine kinase mutations are the leading biomarkers. Dr. Fred R. Hirsch from the University of Colorado Cancer Center presented new data about the utility of these biomarkers from the patients with available tissue participating in the ISEL study, a phase III randomized, placebo-controlled trial of salvage gefitinib. Patients with high EGFR polysomy or true gene amplification as determined by fluorescence in situ hybridization (FISH), together termed FISH+, trended toward prolonged survival when treated with gefitinib compared with placebo (hazard ratio [HR] 0.61, 95% confidence interval [CI] 0.36-1.04). This suggests that EGFR FISH is a useful method to predict survival with TKI therapy, as was seen in the molecular subgroup analysis of the BR.21 erlotinib trial and in other retrospectively analyzed cohorts of gefitinib-treated patients. Furthermore, Dr. Hirsh found that, in the ISEL trial, EGFR protein expression measured by immunohistochemistry staining (IHC) could identify a subset of patients that trended toward a survival benefit from gefitinib therapy (HR 0.77, 95% CI 0.56-1.08). However, the benefit in IHC+ patients was not as striking as that in FISH+ patients.

Dr. Frances Shepherd from the University of Toronto presented new data on the molecular analyses of the BR.21 trial. Additional patient tumor samples have been added to her analysis since the original publication by Tsao and colleagues. Furthermore, it included only the classically described mutations, exon 19 deletions and exon 21 leucine to arginine substitution at codon 858 (L858R), in response to criticisms that Tsao et al.’s article included a high number of novel mutations. Dr. Shepherd reported that the proportion of tumors harboring a classic EGFR mutation was 11.9% and that EGFR mutation-positive patients did not achieve a survival benefit from erlotinib therapy compared with placebo (HR 0.64, 95% CI 0.24-1.75). Furthermore, patients with increased gene copy number (FISH+) had a higher response rate to erlotinib therapy compared with FISH- patients (20% versus 2.4%; P = 0.03) and a survival benefit with erlotinib treatment compared with placebo (HR 0.44, 95% CI 0.2-0.82). Dr. Shepherd also emphasized the value of testing EGFR protein expression by IHC. She presented a combined analysis with the molecular data from the ISEL, BR.21, and IDEAL (two phase II studies with gefitinib) trials. IHC+
patients from these three cohorts had a higher response rate to TKI therapy compared with IHC- patients (10.9% versus 3.0%; P = 0.003).

Dr. Bruce Johnson from the Dana-Farber Cancer Institute discussed clinical situations in which EGFR mutation testing might be clinically relevant and emphasized the importance of prospectively identifying patients that may dramatically benefit from TKI therapy and of molecular characterization of acquired resistance to EGFR TKIs. EGFR mutations have been retrospectively associated with increased response rate and survival benefit from TKI therapy, but these findings need to be validated in clinical trials enrolling a molecularly selected population. In addition, prospective studies are needed to confirm reports that suggest survival may be increased for exon 19 deletion mutation patients treated with EGFR TKIs compared with L858R point mutation patients. Finally, Dr. Johnson pointed out that new technologies are being developed that can rapidly detect mutations with unprecedented sensitivity.

**EGFR TYROSINE KINASE INHIBITORS IN COMBINATION WITH OTHER AGENTS**

There is a strong precedent for targeted therapeutics to demonstrate enhanced activity when used in combination with chemotherapy, as seen with chemotherapy and trastuzumab in breast cancer, cetuximab in colon cancer, bevacizumab in colon cancer, and bevacizumab in NSCLC. However, four large randomized trials of first-line combination chemotherapy plus an EGFR TKI for NSCLC including more than 4000 patients in total each failed to show an advantage to this strategy. Dr. David R. Gandara from the University of California at Davis discussed potential explanations for the failure of first-line EGFR TKIs with chemotherapy. He posited that lack of proper patient selection, via the molecular strategies discussed above, could account for the negative results. If an insufficient number of patients with markers of TKI-responsive disease were recruited for the studies and/or were randomized to the TKI arms, a true treatment benefit may have been missed. Retrospective analyses to validate this theory have been limited or inconclusive because only a few patients enrolled in clinical trials have available archived tissue for molecular analysis. There is indirect evidence that a randomized trial with more stringent patient selection could show a survival benefit. In a prespecified subset analysis of the TRIBUTE trial of carboplatin and paclitaxel combined with erlotinib or placebo, never-smokers (a patient characteristic associated with EGFR mutations) achieved a survival benefit with erlotinib treatment compared with placebo.

A second explanation for the lack of benefit from combination therapy is that EGFR TKIs could have a negative interaction or antagonism when given with chemotherapy, at least in a subset of patients. Dr. Gandara hypothesized that EGFR TKIs induce apoptosis only in EGFR-mutated NSCLC and induce cell cycle arrest in wild-type tumors. Because chemotherapy is active in the S and M phases of the cell cycle, wild-type cells in G1 arrest because of constant TKI exposure may be less responsive to chemotherapy. There is preclinical evidence to support this theory. EGFR TKIs induce apoptosis in NSCLC cell lines known to harbor a mutation but not in wild-type cell lines. Furthermore, NSCLC cell lines and xenograft models exposed to concurrent continuous EGFR TKI and chemotherapy undergo less cell kill compared with sequential or intermittent exposure. Because most patients in these trials are presumed to have wild-type EGFR, this mechanism could have had a major impact on the trial results. There are ongoing prospective trials examining sequential and pharmacodynamically separated chemotherapy and EGFR TKIs to further understand the interaction.

Concurrent use of EGFR TKIs with the anti-inflammatory cyclooxygenase-2 (COX-2) inhibitors was discussed by Dr. Karen Reckamp from the University of California at Los Angeles. COX-2 overexpression is seen in many malignancies, including NSCLC, and leads to increased prostaglandin E2 (PGE2) levels, which in turn promote many features of tumorigenesis, such as angiogenesis, metastasis, and resistance to apoptosis. PGE2 can stimulate cancer cell growth via Erk-mediated signaling, which is independent from the EGFR pathway, and suggests that the COX-2/PGE2 pathway may be important in clinical EGFR TKI resistance. In addition, PGE2 inhibits E-cadherin expression, which has been shown to diminish sensitivity to EGFR TKIs. Dr. Reckamp presented results from a phase I trial using the COX-2 inhibitor celecoxib in combination with erlotinib in patients with NSCLC. The combination was well tolerated, and early analyses show that some patients with wild-type EGFR tumors have a partial response to celecoxib plus erlotinib. Phase II studies of this combination are ongoing.

**ANTI-EGFR MONOCLONAL ANTIBODIES**

The anti-EGFR monoclonal antibodies most advanced in clinical development in NSCLC include cetuximab (C225), matuzumab (EMD720000), and panitumumab (ABX-EGF). Dr. Edward Kim from the MD Anderson Cancer Center reviewed the current state of clinical development of cetuximab in NSCLC. Cetuximab is a chimeric IgG1 antibody approved for the treatment of colorectal and head and neck cancers. It induces antibody-dependent cell cytotoxicity. Cetuximab is currently being studied as part of first-line combination therapy for NSCLC in a phase III registration trial (EMR-046) in which patients are randomized to cisplatin and vinorelbine with or without cetuximab. The design of this study was based on a randomized phase II trial with the same treatment arms as second-line therapy that demonstrated promising response rates of 35% and 28% in patients treated with chemotherapy plus cetuximab and chemotherapy alone, respectively. In addition, cetuximab is being studied as combination therapy in patients with chemo-refractory NSCLC in a randomized trial (IMCL-0425) using paclitaxel or docetaxel, plus or minus cetuximab, based on a 27% response rate and a 7.5-month median survival seen with docetaxel and cetuximab in a phase II study. Dr. Kim also noted that, among several studies with cetuximab in advanced cancer patients, the severity of rash has been correlated with...
survival, suggesting that biomarkers of the EGFR pathway may help us to better select patients for treatment.

Dr. Joan Schiller from the University of Wisconsin discussed other EGFR targeted antibodies in clinical development. Matuzumab is a humanized IgG1 antibody, and panitumumab is a human IgG2 antibody. They are both less likely than cetuximab to induce human anti-murine antibody (HAMA) responses, and therefore do not require hypersensitivity premedication. Like cetuximab, matuzumab can induce antibody-dependent cell cytotoxicity, whereas panitumumab cannot. The different properties of these compounds are difficult to assess clinically, especially in light of their unproven clinical role in NSCLC management. Phase I data among patients with treated with matuzumab in combination with every 3-week paclitaxel at 175 mg/m² were recently reported. The combination was well tolerated, and four of 18 patients responded. Dr. Schiller presented a proposed three-arm randomized phase II study evaluating pemetrexed, and pemetrexed plus matuzumab at either 800 mg weekly or 1600 mg every 3 weeks as second-line treatment of advanced disease. Panitumumab was studied as first-line therapy with paclitaxel and carboplatin in as phase I/II trial. Although the triplet seemed to be well tolerated, the phase II portion of the trial including 166 patients randomized to chemotherapy plus or minus panitumumab did not show a difference between the arms in response rate, median time to progression, or survival. Molecular analyses of EGFR and K-ras mutations performed in tumors from 88 participants of this study did not show any association with response data.

There are several important questions to be answered about anti-EGFR monoclonal antibodies in lung cancer, including comparisons among the different antibodies in terms of safety and efficacy, mechanisms underlying the association of skin rash and treatment benefit, and outcomes of combinations with cytotoxic therapy and other targeted agents. Correlative studies of biomarkers that may predict treatment benefit from these agents are also strongly needed.

IRREVERSIBLE EGFR INHIBITORS

Somatic activating EGFR mutations occur in only a small population of patients with NSCLC, but they correlate with dramatic responses to EGFR TKI therapy. The secondary acquired resistance mutation T790M has been described in some patients with activating mutations that initially responded to EGFR TKI therapy but subsequently relapsed. The T790M mutation introduces a bulky residue at the TK ATP-binding site, hindering TKIs from reaching the target. However, it is not present in all TKI-resistant patients, and there are several possible mechanisms of developing clinical TKI resistance. Dr. Thomas Lynch from the Massachusetts General Hospital Cancer Center discussed TKI resistance and new strategies for resistant patients currently under clinical investigation. In preclinical models, gefitinib-sensitive cell lines can be used to generate TKI-resistant clones via continuous long-term exposure to the drug. These gefitinib-resistant clones undergo significant cell kill by investigational irreversibly bound EGFR TKIs such as HKI-272, EKB-569, and HKI-357. It is thought that these TKIs are able to overcome the steric hindrance from T790M mutations and may also be able to combat other mechanisms of resistance, such as altered receptor trafficking. Furthermore, it was not possible to generate clones of cells that were resistant to irreversible TKIs, even with prolonged high-dose exposure. These findings are analogous to other cancers (chronic myelogenous leukemia and gastrointestinal stromal cell tumors) that are dependent on mutated TK signaling and initially demonstrate sensitivity to inhibitors but subsequently develop resistance. In these cases, compounds that can overcome the resistance mutations in vitro have been shown to be clinically useful. Therefore, Dr. Lynch concluded that molecular profiling of NSCLC tumors may be a useful strategy for identifying cases that are potentially sensitive to irreversible TKIs and may be clinically useful in both TKI-naïve patients and those previously treated with reversibly bound TKIs. To validate this approach, there is an ongoing multicenter phase II trial with the HKI-272 compound that stratifies patients based on their EGFR mutational status and their prior TKI exposure.

CONCLUSIONS AND FUTURE DIRECTIONS

EGFR TKIs have become a foundation in the treatment of chemo-refractory NSCLC. The role of EGFR-targeted kinase inhibitors and monoclonal antibodies in the management of NSCLC continues to be refined, and new studies are being launched in early-stage disease and in adjuvant settings. Significant progress in translational research is leading to the discovery of biomarkers to guide patient selection for these treatments, the potential enhancement of activity through combination with other treatment modalities, and the clinical development of novel EGFR inhibitors. Continued efforts in these areas will enable us to offer more effective therapy options to our patients. A “bench to bedside” approach with rapid validation of biological hypotheses through well-designed clinical trials is essential to achieve this goal.

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