Resistance to Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors

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The epidermal growth factor receptor (EGFR) has become an important target in the treatment of non-small cell lung cancer (NSCLC). A number of drugs have been developed that are designed to inhibit EGFR including a monoclonal antibody, cetuximab, and small molecule tyrosine kinase inhibitors (TKIs) such as gefitinib and erlotinib. Mutations in EGFR and K-*ras* and EGFR expression by immunohistochemistry (IHC) and fluorescent in situ hybridization (FISH) have all been evaluated as scientific correlates in trials using these agents. There is great interest in understanding the clinical parameters and biomarkers that predict for survival benefit and drug resistance.

SUMMARY OF PRESENTATIONS

The EGFR-TKIs have usually been used in the second-line setting, and biomarkers have been evaluated in an exploratory fashion. In the ISEL trial that compared gefitinib with placebo, both EGFR mutations (exon 19 deletion and exon 21 L858R) and EGFR high copy number predicted for higher response rate.[1] The INTEREST trial compared gefitinib to docetaxel in a similar patient population.[2] Again the response rate was higher for patients treated with gefitinib who were EGFR mutation+ or FISH+. Overall survival was similar for gefitinib and docetaxel irrespective of EGFR gene copy, EGFR protein expression, EGFR, or K-*ras* mutational status. Interestingly, EGFR mutations did predict for a better progression-free survival for patients treated with gefitinib on both trials. In the IPASS trial, east Asian patients who were never or light smokers were randomized to receive chemotherapy or gefitinib as first-line treatment.[3] Patients who were EGFR mutation+ benefited more from gefitinib, whereas the mutation negative patients did better with chemotherapy, indicating a role for mutation testing if an EGFR-TKI is used as initial treatment.

The EGFR-TKIs have not been successfully combined with chemotherapy in unselected, untreated patients. A randomized phase II trial prospectively selected patients who were EGFR IHC+ and/or EGFR FISH+ to receive erlotinib or erlotinib and chemotherapy.[4] Activating EGFR mutations and absence of K-*ras* both suggested a better survival for all patients, whereas EGFR FISH+ patients trended toward a better survival with erlotinib.[5] The MARVEL trial will categorize patients receiving second-line therapy on the basis of EGFR FISH. Both positive and negative patients will be independently randomized to receive either pemetrexed or erlotinib.

Cetuximab as an antibody to EGFR may work differently from the TKIs. On S0342, chemotherapy was combined with concurrent or sequential cetuximab.[6] Although there was little difference in outcome between the two study arms patients who had a high EGFR, copy number by FISH had a better response rate and survival. Two phase III trials, FLEX and BMS 099, combined chemotherapy ± cetuximab in the treatment of chemonaive patients with NSCLC.[7,8] Patients on the FLEX trial had to be EGFR+ by IHC and patients who received the cetuximab had a modest but significant survival benefit. On the BMS 099 trial, there was no patient selection and no survival advantage for the cetuximab arm. A number of molecular markers were evaluated on the BMS trial, and none of the markers including EGFR FISH and K-*ras* were predictive of benefit or lack there of. It is clear that validation of the EGFR FISH biomarker is warranted.

There are a number of other large trials that are using the EGFR-TKIs. Many of these trials are collecting tissue and serum and stratifying patients for molecular markers in an attempt at validation of their predictive potential. In the TITAN trial, patients are treated with standard platin-based chemotherapy. Those who progress are randomized to chemotherapy or erlotinb, whereas those who do not progress (SATURN) are randomized to placebo or maintenance erlotinib. The ATLAS trial is evaluating erlotinib + bevacizumab versus bevacizumab as maintenance after initial chemotherapy.

There are now a number of new generation EGFR inhibitors. BIBW 2992 is an oral irreversible TKI of both EGFR and HER2, and it demonstrates activity in EGFR mutants resistant to erlotinb, gefitinib, and lapatinib. It has demonstrated single agent activity in patients with EGFR mutations (LUX-Lung 2), and a trial is underway evaluating the drug in EGFR TKI failures (LUX-Lung 1). Additional trials are planned comparing the drug with chemotherapy as initial treatment and combining it with cetuximab in patients who have developed resistance to gefitinib or erlotinib. IMC-11F8 is a fully human IgG1 antibody with an epitope similar to cetuximab. It is currently being evaluated in clinical trials

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in colon and lung cancer. IMC-3G3 is an antibody against PDGFRα currently in phase I evaluation. Phase II trials are being planned in a number of tumor types. EVRI (BMS-690514) is a dual inhibitor of ErbB and VEGFR2 and is a potent inhibitor of EGFR and VEGFR signaling. In a phase I trial with a phase II expansion in NSCLC toxicities were manageable, and there was activity in erlotinib naive and refractory patients. Phase I trials in combination with chemotherapy are being planned in NSCLC and colon cancer. PF-00299804 is a PanHER TKI that is a potent inhibitor of all HER receptor TKs and has activity in sensitive and resistant EGFR/HER2 driven xenograft models. In a phase II expansion trial in NSCLC after phase I, the drug had activity in patients with T790M mutations. There are a number of ongoing phase II trials in NSCLC in erlotinib refractory patients, second/third line versus erlotinib, and first line in never or light smokers.

FUTURE DIRECTIONS

It is of utmost importance to determine the molecular markers that define sensitivity and resistance to EGFR inhibitors. This is difficult because of inconsistencies among techniques and laboratories used to determine various biomarkers and the lack of patient tumor tissue. Molecular characterization of circulating tumors cells may provide a strategy for noninvasive monitoring of tumor genotypes during treatment.[9] By using a microfluidic device containing microposts coated with antibodies against epithelial cells, EGFR mutations can be detected accurately from circulating tumor cells. Matrix-assisted laser desorption ionization mass spectrometry has been used on patient serum to identify those likely to benefit from EGFR TKIs.[10] S0709 is a phase II trial of erlotinb ± chemotherapy in proteomic positive NSCLC patients. These new technologies and new drug development along with rational clinical trial designs will hopefully advance the field and improve the treatment of lung cancer.

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