genetic polymorphisms could affect the treatment response and might be used as genetic marker of tumor response after radiation therapy.

Session M03: Molecular Predictors of EGFR TKIs

M03-01 Molecular Predictors of EGFR TKIs, Mon, Sept 3, 10:30 - 12:00

Molecular predictors of EGFR-TKIs

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Subsets of patients with non-small cell lung cancer (NSCLC) respond remarkably well to small molecule tyrosine kinase inhibitors (TKI) specific for epidermal growth factor receptor (EGFR) such as gefitinib or erlotinib. Those patients are typically of East Asian ethnicity, female gender, no history of smoking or those with adenocarcinoma. In 2004, it was found that NSCLC occurring in patients with above-mentioned characteristics frequently harbors activating mutations of the EGFR gene. Of note, EGFR mutation is a first molecular alteration in NSCLC that is more frequent in never smoking patients. Our case-control study indicated that EGFR mutations occurred independent of smoking and apparent inverse relationship with smoking was due to dilution by tumors without EGFR mutations that increased with smoking history. In general, about 80% of NSCLCs with EGFR mutations respond to EGFR-TKIs, whereas some 10% of tumors without the mutations do so. Several investigators claim that EGFR gene copy number is more predictive of response or survival, although at least in our cohort, EGFR mutations were far better than copy number. In addition, various predictive markers have been reported to date. Those include expression of ligands for EGFR, change in other HER family genes including HER2 mutation or downstream molecules of EGFR pathway (e.g., KRAS mutation, AKT phosphorylation, PTEN expression, etc.).

It is common for patients to show disease progression after presenting with an initial marked response to EGFR-TKIs. Secondary mutation occurring in exon 20 of the EGFR gene (T790M) has been associated with the acquired resistance to EGFR-TKI. We were able to confirm that 7/14 patients with acquired resistance after initial dramatic response had T790M, but that no novel mutations were found. New class of TKIs that are able to overcome T790M are currently being developed. Very recently, Engelman et al. reported that amplification of the MET gene is another mechanism of acquired resistance of EGFR-TKI through activation of HER3 signaling. It is known that some NSCLCs have T790M or MET amplification even before EGFR-TKI therapy. Obviously, these NSCLC would require another treatment strategy. Since all but one phase III trials have failed to show a survival advantage of the treatment arm involving EGFR-TKIs, it appears mandatory to select patients by several of above-mentioned biomarkers. Through these efforts, it would be possible to individualize EGFR-TKI treatment for patients suffering from lung cancer.

References


M03-02 Molecular Predictors of EGFR TKIs, Mon, Sept 3, 10:30 - 12:00

Molecular predictors for epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs): role of egfr gene amplification

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Worldwide, lung cancer is responsible for more than one million death per annum and is the leading cause of cancer mortality. Most patients with lung cancer are not cured and the overall 5-year survival rate is approximately 15%. Recent advances in the knowledge of cancer biology led to the identification of several potential molecular targets that play a key role in cancer development and progression. Selective targeting of cancer cells based on their molecular phenotype can provide effective anti-cancer activity avoiding the commonly experienced side effects induced by chemotherapy. The new agents range from antibodies that form complexes with antigens on the surface of the cancer cell to small molecules that have been engineered to block key enzymatic reaction. The interaction of the drug with its target inhibits pathways that are essential for cell proliferation or activates pathways that culminate in cancer cell apoptosis. So far, the dominant clinical trial strategy for patients with Non-Small-Cell Lung Cancer (NSCLC) has been to include a generic population of patients, with no selection based on biological criteria and, most importantly, with none or poor target assessment. Although recent clinical trials in NSCLC have demonstrated survival improvement without a defined biological endpoint, the hazard of continuing to perform clinical trials without any patient selection carries the risk of administering the wrong drug to the wrong patient and considering ineffective a drug that could dramatically improve the outcome of some patients, even if those are numerically small. The Epidermal Growth Factor Receptors (EGFRs) stand at the origin of a major signaling pathway involved in the growth of lung cancer. The EGFR superfamily includes four distinct closely related transmembrane receptors: EGFR/erbB-1, HER2/erbB-2, HER3/erbB-3, and HER4/erbB-4. EGFR is normally found on the surface of epithelial cells and has been found to be commonly overexpressed in a variety of human malignancies. Different ligands can lead to EGFR activation and subsequent signal transduction, including the epidermal growth factor, the transforming growth factor alpha and neuregulins. After ligand binding to the extracellular receptor domain, EGFR undergoes homo- or heterodimerization and autophosphorylation of its intracellular tyrosine kinase domain. These autophosphorylation events trigger a cascade of downstream signals, which ultimately result in an increase of cellular
motility, proliferation and invasion, and a block of apoptosis, contributing to cancer development and progression. Gefitinib (ZD 1839, Iressa™, AstraZeneca, UK) and erlotinib (OSI 774, Tarceva™, Genentech, US) are orally active, selective EGFR Tyrosine Kinase Inhibitors (EGFR-TKIs) that demonstrated anti-tumor activity in a variety of human cancer cell lines overexpressing EGFR. The encouraging results observed in phase II studies and the survival improvement observed in phase III trials in certain subgroup of patients indicate that these drugs are particularly effective in individuals with particular clinical or biological characteristics. Several clinical features were found associated with increased response or survival to EGFR-TKIs, including never smoking history, female gender, adenocarcinoma histology and Asian ethnicity. During the last three years, biological predictors for EGFR-TKI sensitivity have been discovered. In 2004, three groups have shown that mutations in the TK domain of EGFR were associated with response of NSCLC to gefitinib or erlotinib. These mutations were somatic and more frequently observed in patients with clinical features known to be associated with TKI sensitivity, such as female gender, adenocarcinoma histology, Asiatic ethnicity and never smoking history. Many types of mutations have been reported, but so far only four drug-sensitive mutations have been validated. The most common EGFR drug-sensitive mutations are exon 19 deletions and exon 21 L858R substitution, together accounting for about 85% of all EGFR mutations in NSCLC. Other less frequent EGFR mutations include substitutions in exon 18 (G719A/C) and 21 (L861Q). Several other EGFR gene mutations have been described but their role is not clear, and it is not possible to exclude that some of them are artefacts. Although several retrospective and prospective studies showed that patients with EGFR mutations, particularly individuals harbouring exon 19 deletion, respond to TKIs, the impact on survival is unclear because of the possible prognostic rather than predictive value of such mutations. Survival analysis of the largest trials with TKIs showed no survival benefit for patients harbouring EGFR mutations receiving a TKI, suggesting a possible prognostic impact. In the randomized placebo-controlled trial comparing erlotinib to placebo (BR21), presence of EGFR mutations did not predict for a survival benefit from the TKI therapy, even if mutation analysis was restricted to patients harbouring the most frequent EGFR mutations (exon 19 deletion and exon 21 L858R substitution). Since the first reports, clearly emerged that a significant fraction of patients with EGFR mutations (12%-84%) do not respond to TKIs, suggesting that other mechanisms are involved in TKI sensitivity. Four studies evaluated EGFR gene copy number by Fluorescence In Situ Hybridization (FISH). In the Italian study, individuals with EGFR high polysomy or gene amplification (defined as EGFR FISH positive) had a significantly higher response rate, and a significantly longer time to progression and survival than patients with no EGFR gene gain (defined EGFR FISH negative). In the randomized placebo-controlled phase II study of erlotinib versus placebo, EGFR FISH positive patients treated with erlotinib had higher response rate and longer survival than EGFR FISH positive treated with placebo (HR 0.44, p=0.008), whereas there was no advantage determined by the drug in FISH negative patients. The randomized placebo-controlled phase III study of gefitinib versus placebo (ISEL) confirmed the better outcome in terms of response rate and survival for EGFR FISH positive patients treated with gefitinib than EGFR FISH positive treated with placebo, with no survival difference in EGFR FISH negative irrespective of the treatment. In the SWOG S0126 trial, where patients with bronchiolo alveolar carcinoma (BAC) were treated with gefitinib 500 mg/day, Hirsch et al. observed longer survival for EGFR FISH positive patients over those who had no gene gain (HR 2.02, p=0.042). More recently, the ONCOBELL trial, a prospective phase II study evaluating response rate in EGFR FISH positive or never smoker patients treated with gefitinib confirmed that EGFR FISH testing is useful for patient selection. In this study, response rate was 68% in EGFR FISH positive and no response was observed in never smokers negative for EGFR FISH and mutation. Response and survival improvement observed in EGFR FISH positive patients indicate that TKI therapy should be offered to patients with such biological characteristic. Because gain in copy number of the EGFR gene was associated with survival, and because FISH is readily available clinical test, the EGFR FISH analysis represents an ideal test for selecting patients candidate to TKI therapy.

M03-04 Molecular Predictors of EGFR TKIs, Mon, Sept 3, 10:30 - 12:00

Selecting lung cancer patients to targeted therapies based on protein expression by immunohistochemistry

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Targeted therapies directed against epidermal growth factor receptor (EGFR) are effective in a subset of non-small cell lung cancer (NSCLC) patients, however the survival advantage in unslected populations is relatively modest (1, 2). Numerous tissue and serum based markers have been proposed as predictors of survival and response benefit from EGFR inhibitors. EGFR gene copy number and mutation analyses are now being explored in prospective clinical studies in enriched populations. These assays are very promising, however costly and not widely available. In contrast, protein expression studies by immunohistochemistry are routinely performed in many laboratories for selection of breast cancer patients to hormonal therapy and HER2 inhibitor trastuzumab.

The value of EGFR protein expression as a predictor of sensitivity to EGFR inhibitors is debated. Depending on the analyzed cohort, staining protocol and cut-off point, EGFR protein positivity is observed in approximately 60% - 90% of patients. Analyses from phase II clinical studies with gefitinib concluded that EGFR protein expression is not associated with increased response rates or prolonged survival (3). Phase III clinical studies with erlotinib versus placebo in combination with chemotherapy followed by maintenance erlotinib/placebo did not show any association of outcome and EGFR protein expression (4, 5). It may be concluded from these studies that concurrent treatment with EGFR tyrosine kinase inhibitors (TKIs) and chemotherapy is equally ineffective in EGFR positive (EGFR+) and EGFR negative (EGFR-) patients. Results of NSCLC monotherapy trials with gefitinib or erlotinib indicated that approximately 8 - 13% of EGFR+ as compared to 2-5% of EGFR- chemotherapy-pretreated patients respond to these agents. Moreover, some survival improvement was observed in EGFR+ patients in prospective monotherapy studies (BR.21 trial - hazard ratio [HR]: 0.68, 95% confidence interval [CI]: 0.49 - 0.95, p=0.02; ISEL trial - HR: 0.77, 95% CI: 0.56 - 1.08, p=0.126) whereas no survival advantage was shown in EGFR- patients (6, 7). Detailed analysis of cut-off points to define EGFR protein positivity based on BR.21 and ISEL trials with erlotinib and gefitinib, respectively, indicated that low cut-off points (i.e. 10% of cells with positive staining of any intensity) were better discriminators of survival advantage than higher cut-off points (8, 9). Other single-arm studies indicated that EGFR protein expression is associated with outcome independently from other biologic features (10, 11). In a combined cohort of gefitinib treated patients, EGFR+ patients for both gene copy number and protein expression had a median survival of 21 months, patients with single positive test - 11 months and