MTP10-01 **EGFR-Targeted Therapy, Tue, Sept 4, 07:00 - 08:00**

Impact of genomic changes on the treatment of lung cancer

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Three years have passed since mutations of the tyrosine kinase domain of the epidermal growth factor receptor (EGFR) were discovered in patients with lung cancer who had dramatic clinical responses to treatment with gefitinib. Additional laboratory and clinical studies have provided further insights into the biological impact of EGFR mutations in cell culture experiments and in patients with lung cancer. In vitro characterizations of lung cancer cell lines and host cell lines transfected with these mutant and wild type EGFRs show most cell lines with mutated EGFRs are growth inhibited by 10-100 fold lower concentrations of gefitinib and erlotinib (10-100 nM) compared to wild type EGFR (Approximately 1-5 uM). Lung cancer cell lines with mutations of the EGFR treated with concentrations of gefitinib and erlotinib that are achievable in the plasma undergo apoptosis rather than growth arrest. The other common genomic changes that arise in adenocarcinomas of the lung that have an impact on tyrosine kinase inhibitors and other targeted agents include KRAS, BRAF, and LKB1.

Prospective studies of lung cancer patients with EGFR mutations treated with gefitinib and erlotinib have reported a close association between EGFR mutations, increased chance of clinical response and longer survival. Patients with EGFR mutations treated with gefitinib or erlotinib have a response rate of approximately 80%, a median time to progression in excess of approximately one year, and a median survival in excess of two years. This has led to the development of commercial tests to determine if the DNA from tumors retrieved from patients with adenocarcinoma have a mutation of the EGFR.

The genomic change associated with resistance to treatment with gefinib and erlotinib is a DNA mutation which changes the threonine to methionine at the 790th amino acid of EGFR known as the (T790M) mutation as well as amplification of the MET oncogene. Irreversible inhibitors including HKI-272 and PF-299804 can cause growth inhibition in NSCLC cell lines with both the resistance and sensitizing mutations, while gefitinib and erlotinib do not. HKI-272 and PF-299804 entered directed phase I and phase II trials in patients previously treated with gefitinib and erlotinib and we await the results of the trials.

MTP11-01 **Pulmonary Toxicity of Therapy, Tue, Sept 4, 07:00 - 08:00**

Pulmonary toxicity of therapy

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The toxicities of dyspnea, hypoxia, pneumonitis, and/or fibrosis related to thoracic radiotherapy have been observed for many years. Toxicities are generally graded by using the NCI Common Toxicity Criteria or the WHO toxicity criteria (http://www.fda.gov/cder/cancer/toxicityframe.htm). Dose-volume histograms have been developed to evaluate the volume of lung receiving various doses of radiation. The V_{20} is the percentage of lung volume that receives a radiation dose of 20 Gy or more. In general, the larger the V_{20} volume, the higher the risk of radiation pneumonitis, and V_{20} volume of 35% or more are associated with high risk of acute radiation pneumonitis and late scarring (1). Acute radiation pneumonitis occurs within 1-3 months of radiotherapy, and may develop in 5-15% of patients. Direct injury to endothelial and epithelial cells may result in radiographic findings of pulmonary infiltrates in the field of radiation, but also "out of field" responses have been described and biopsies demonstrate a bronchiolitis obliterans organizing pneumonitis (BOOP) like reaction (also called cryptogenic organizing pneumonia – COP). The RTOG evaluated acute and late (90 days from start of RT) pulmonary toxicities associated with 5 completed trials of thoracic radiotherapy with sequential or concurrent chemotherapy (2). Acute pulmonary toxicity of grade 3 or greater occurred in 4-7% of participants. Late pulmonary toxicities occurred in 10-21% of patients. Severe late lung toxicity was greater in trials with concurrent chemotherapy and hyperfractionated RT, as well as induction chemotherapy followed by concurrent chemoradiotherapy (one daily). Sequential chemotherapy and radiotherapy had lower rates of late pulmonary toxicity (10%). Stereotactic body radiation therapy (SBRT) is being utilized with increasing frequency, especially for medically inoperable lung cancer patients. With this technology, large dose fractions are given to very localized fields. In a phase II trial of SBRT, investigators administered 60-66 Gy in 3 fractions over 1-2 weeks (3). Grade 3-5 toxicity occurred in 14 of 70 patients enrolled. Toxicity was greater with centrally located tumors as compared to the peripheral cancers. There were 6 treatment related deaths. Four of these deaths were associated with pneumonia. This increased toxicity with centrally located tumors is due to bronchial stenosis and scarring due to the high dose of radiation.

Gemcitabine

Gemcitabine pulmonary toxicity has been reported in 1-3% of patients treated with this agent and may be fatal. The CT features include ground-glass opacities, thickened septal lines and reticular opacities. The distribution is diffuse and bilateral. Gemcitabine pulmonary toxicity may be difficult to differentiate from viral pneumonitis. It is important to discontinue treatment as soon as it is suspected because an additional treatment may prove to be fatal. In severe cases, corticosteroids are usually given although their efficacy is uncertain.

Gemcitabine is a potent radiation sensitizer with recall phenomena. The maximum dose of gemcitabine given with concurrent thoracic radiotherapy is substantially attenuated, from the usual doses when given alone, because of the risk of pneumonitis. In a phase I trial of the CALGB, the maximum tolerated dose of twice weekly gemcitabine was 35 mg/m^2 (70 mg/m^2/week) given with concurrent thoracic radiotherapy (4). In a phase II trial with gemcitabine (600 mg/m^2 on d 1, 8) and cisplatin given concurrent with thoracic radiotherapy, grade 3-4 dyspnea was observed in 14 of 62 (23%) of participants (5).

Taxanes

The taxanes, paclitaxel and docetaxel, are widely used in treatment of lung cancer. Acute type I hypersensitivity reaction with paclitaxel are well known. Pulmonary infiltrates following treatment have been reported in low frequency with paclitaxel and somewhat more cases following docetaxel treatment. Docetaxel has also been associated with the development of pleural effusions. The combination of docetaxel and gemcitabine has been tested in a phase II trial by Japan Lung Cancer Cooperative Group. They observed an unexpectedly high rate of grade 3 interstitial lung disease of 11% (7 of 63 patients) with this combination (6). Others have also reported high pulmonary toxicity with this combination. Sekine and associates observed pneumonitis in 24% (14 of 59) of Japanese patients treated with consolidative docetaxel following concurrent chemoradiotherapy with other agents (7). Similarly, the Hoosier Oncology Group reported pulmonary toxicity in 10% of patients receiving consolidative docetaxel (8).