	N	PR	SD	PD	NE	TTP, months	OS, months
EGFR: exon 19 del	17	12	3	-	1	16.6	> 24
EGFR: L858R	8	3	5	-	-	9.7	14.6
KRAS: codon 12 mutations	20	-	9	9	2	3.8	15.5
KRAS: other mutations	4	-	1	2	1	1.2	3.3

Conclusion: The role of specific EGFR and KRAS genotype merits further continued investigation. As several trials of first-line gefitinib or erlotinib near completion, the ability to combine mutation data and clinical outcomes from increasing numbers of chemotherapy-naïve patients in a web-based database may yield more powerful insight into roles of specific mutations and help guide treatment decisions. We anticipate the addition of a number of patients from Japan and from other trials in the coming months.

D2-07 Molecular Targeted Therapy: Biomarkers, Thu, 12:30 - 14:15

Mechanisms of activating PI3K signaling in lung cancers that become resistant EGFR tyrosine kinase inhibitors

Engelman, Jeffrey A.; Zejnullahu, Kreshnik; Mitsudomi, Tetsuya; Hyland, Courtney; Park, Joon Oh; Lindeman, Neal; Gale, Christopher-Michael; Zhao, Xiaojun; Christensen, James; Rogers, Rogers M.; Cappuzzo, Federico; Mok, Tony; Lee, Charles; Bruce, Johnson E.; Cantley, Lewis C.; Jänne, Pasi A.

Massachusetts General Hospital Cancer Center, Boston, MA, USA

Background: Cancers that are sensitive to EGFR inhibitors down-regulate Phosphoinositide 3-Kinase (PI3K) signaling in response to these drugs. Inhibition of PI3K signaling appears to be critical for ErbB inhibitors to induce cell death. Although lung cancers with EGFR mutation often have initial impressive responses to EGFR inhibitors, they invariably develop resistance. In 50% of such patients, a single secondary mutation, a substitution of methionine for threonine at position 790 (T790M), has been identified. EGFR T790M is sufficient to cause gefitinib resistance and leads to persistent ERBB3/PI3K/Akt signaling in the presence of gefitinib. However, the mechanisms by which the other half of cancers becomes resistant remain unidentified.

Methods: To identify novel mechanisms of resistance, we cultured highly sensitive EGFR mutant and amplified cell lines in the presence of increasing concentrations of gefitinib until resistant cell lines were produced.

Results: We found that, unlike the parental cells, all of the resistant cell lines maintain PI3K signaling in the presence of getitinib. Some cell lines use ErBB3 (i.e. no change from the parental cell line), whereas others utilize new adaptor proteins. Blocking the new mechanisms of activating PI3K leads to cellular death in the resistant cell lines.

Conclusions: Cancers that become resistant to EGFR inhibitors acquire novel mechanisms for activating PI3K. Inhibiting these pathways may be effective methods for treating cancers with acquired resistance to EGFR inhibitors.

Session D3: Pharmacogenomics & Biomarker in Cytotocix Chemotherapy Thursday, September 6

D3-01 Pharmacogenomics & Biomarker in Cytotocix Chemotherapy, Thu, 12:30 - 14:15

Genotyping single-nucleotide polymorphisms(SNP) in ERCC1, XPD, XRCC1, XRCC3 and MDR1 and CCND1 genes for response and toxicity prediction in chemotherapy of non small cell lung cancer (NSCLC)

Pesek, Milos[1] Brùha, Frantiſek[2] Bittenglová, Radka[2] Krákorová, Gabriela[2] Beneſová, Lucie[3] Slováèková, Radka[3] Sampalík, Josef[2] Minárik, Marek[3]

[1] Medical Faculty Charles University,Faculty Hospital, Plzen, Czech Republic [2] Faculty Hospital Plzeò, Plzeò, Czech Republic [3] Genomac International Praha, Praha, Czech Republic

Background and Aim: SNP´s of DNA repair genes as well as SNP´s in MDR1 a CCND1 genes should serve as predictors of response to chemotherapy in NSCLC. The aim of this study was to find SNP´s, their variants and combinations and their correlations to the response and toxicity for various cytostatic schedules.

Material and Methods: Patients were divided according to prescribed cytostatics.There were several segregations,one using groups of patients treated by cisplatin or carboplatin, and another one separating patients treated by taxanes or vinorelbine vs.treated by gemcitabine. SNP´s were screened in DNA isolated from peripheral blood with the help of cycling-gradient capillary electrophoresis technique (CGCE) and standard DNA sequencing of PCR products. The following set of SNP markers was screened in all patients: ERCC1 Asn118Asn (C/T), ERCC2/XPD Lys751Gln (A/C), ERCC2/XPD Asp312Asn (G/A), XRCC1 Arg399Gln (G/A), XRCC3 Thr241Met (C/T), CCND1 A870G and MDR1 C3435T.

Results: The SNP set was screened in a total of 80 NSCLC patients. The group consisted of 57 males and 23 females, aged from 27 - 78 with median 59.9 years. Overall response rates of chemotherapy induced leucotoxicity suffering patients were higher than thosesuffering from chemotherapy induced anaemias and/or thrombocytopenias. For ERCC1 (Asn118Asn), homozygous genotype T/T is associated with higher response rate followed by genotype C/T. The T/T patients also responded better to regimens including carboplatin than cisplatin. For XRCC1 (Arg399 Gln), genotype G/A exhibited more frequent response to chemotherapy than homozygous G/G. For XRCC3 (Thr241Met), homozygous genotype C/C is associated with higher response rate compared to homozygous T/T genotype. The C/C patients responded better to regimens including cisplatin than carboplatin. For MDR1 (Ile1145Ile/C3435T), homozygous genotype C/C is associated with higher response rate compared to homozygous T/T. For CCND1 (Pro241Pro), homozygous genotype A/A is associated with higher response rate compared to homozygous G/G. CCND1 genotype is associated with higher tumour response rate to taxanes/vinorelbine-platinum regimens, while genotype G/A is more sensitive to gemcitabine-platinum derivatives.

Combination of several polymorphic markers seems to deliver promising results in prediction of response as well as toxicity. It enables