EGFR copy number per se can affect the clinical outcome of adenocarcinoma of the lung after surgical resection.

Methods: We analyzed 106 cases of primary pulmonary adenocarcinoma who underwent curative resection and whose paraffin blocks were available. We excluded patients who received preoperative chemotherapy and who were presented with distant metastasis. The EGFR gene copy number was evaluated using fluorescence in situ hybridization (FISH) and its prognostic implication was analyzed along with other clinical risk factors.

Results: There were 43 males and 63 females and the mean age was 59.4 (29-85) years. We detected a high EGFR gene copy number in 39 cases (36.8%), among whom, 8 cases (7.5%) showed amplification. 59.4 (29-85) years. We detected a high EGFR gene copy number in 39 cases (36.8%), among whom, 8 cases (7.5%) showed amplification.

54.6% and that of disease specific survival was 38.2%. The risk factors affecting the overall survival were male gender (p=0.0007), smoking history (p=0.0093), and advanced stage (≥IIA; p=0.0375) in univariable analysis. For disease specific survival, male gender (p=0.0333), absence of bronchioloalveolar feature (p=0.0223), advanced stage (p=0.0016), and amplification of EGFR gene copy (p=0.0295) were risk factors in univariable analysis. In multivariable analysis, advanced stage (p=0.001) and EGFR gene amplification (p=0.014) remained as significant risk factors for poor disease specific survival.

Conclusions: We demonstrated that amplification of the EGFR gene affected the clinical outcome of adenocarcinoma of the lung after surgical resection in terms of disease specific survival. This result provides an important message for the protocol design of future trials using EGFR inhibitor. As EGFR gene amplification itself is a poor prognostic factor for disease recurrence, the EGFR gene copy number should be investigated and analyzed in the context of other clinical risk factors in such clinical trials.

PD2-3-3 Molecular Targets and Prognostic Factors, Tue, 16:00 - 17:30

High correspondence between EGFR mutations in tissue and in circulating DNA form non-small-cell lung cancer (NSCLC) patients (p) with poor performance status (PS)

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Background: We evaluated the correspondence between EGFR mutations in NSCLC tissue and matched serum DNA and the value of EGFR mutations as a serological marker.

Methods: 121 Spanish stage IV NSCLC p received customized first- or second-line erlotinib monotherapy based on the presence of EGFR mutations in the tumor tissue. Serum genomic DNA was obtained from all p prior to erlotinib administration. EGFR exon 19 deletions were studied by length analysis of fluorescently labeled PCR products and the exon 21 L858R mutation by a PCR Taqman assay.

Results: The EGFR mutation status in the serum was consistent with that in the tumor tissue of 82/121 (68%) and of 15/16 p (93.8%) with PS 2 had mutations. Overall, 64.3% of p had an exon 19 deletion and 35.7% had L858R. 78% of mutations were found in females (P=0.01) and 77.6% in never-smokers (P=0.07). Response rate was 88% in p with mutations only in the tumor and 87% in p with mutations in tumor and serum. Complete responses were observed in 20% of p with mutations in tumor and serum vs 4% of p with mutations only in tumor (P=0.09). With a median follow-up of 6.8 months (m) (range, 1.2-17.6), time to progression (TTP) and median survival have not been reached. A trend to better outcome was seen in p without serum EGFR mutations. TTP was longer for p with EGFR exon 19 deletions (not reached) than for p with L858R (7.7 m) (P=0.02). TTP for p with PS 2 with exon 19 deletions was not reached, while it was 2.7 m for p with L858R (P=0.17).

Conclusions: EGFR mutations in serum could be a non-invasive source of information on the genotype of the original tumor cells and could be a useful tool to predict p response to erlotinib, especially in p with poor PS.

PD2-3-4 Molecular Targets and Prognostic Factors, Tue, 16:00 - 17:30

Prognostic and predictive value of apoptosis related factors Fas, FasL and survivin in non small cell lung carcinoma patients enrolled in the IALT Trial

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Background: The International Adjuvant Lung Cancer Trial (IALT) demonstrated an absolute survival rate benefit of cisplatin based chemotherapy of 4% in surgically treated patients with non small cell lung carcinoma (NSCLC). To identify immunohistochemical biomarkers which correlate differently with survival in the chemotherapy and observation group (predictive analysis) we collected 867 paraffin blocks from 28 centers and made a histopathological review allowing selection of 783 tumors recorded as NSCLC with pathological parameters. These tumors came from 401 chemotherapy treated and 382 observation patients. Our aim was to evaluate the potential prognostic and predictive role of 3 non mitochondrial apoptotic factors, the death receptor Fas, its ligand Fasl, and survivin a G2-M cell cycle regulated protein with anti-apoptotic properties.

Methods: Immunohistochemical analysis was performed on 783 paraffin sections with automated immunostainer Ventana using specific polyclonal antibodies Fas C20 and Fasl N20 (Santa Cruz) and survivin R&D. Staining scores (0-300) were obtained by multiplication of the percentage of labeled cells by intensity of staining (1-3). The cut off score for discriminating positive from negative cases was 240 for Fas and Fasl and 60 for survivin.

Prognostic and predictive analysis was based on a Cox model adjusted on stage, type of surgery, histology, lymphoid infiltration, pathological N status, WHO performance status, age, sex, and center. Only p values below 0.01 were considered as significant.

Results: Fas and Fasl immunostaining were cytoplasmic and membraneous. Of 773 exploitable cases with positive internal controls (normal epithelial cells of a score 240-300) 73 % were Fas negative, 49 % FasL negative. Taking germinal cells as positive control 54 % of cases were survivin positive.

Fas and Fasl were positively correlated (distribution and intensity) with a Spearman’s correlation of 0.43 (p<0.0001). Survivin did not correlate with Fas, Fasl or P53.

In a logistic model with all variables, Fas positivity correlated with vascular invasion (p=0.006; lower in vascular invasion) and WHO status (p=0.008; higher in low WHO). FasL correlated with histology (p<0.0001; higher in adenocarcinoma) and pleural invasion (p=0.04). Survivin was lower in adenocarcinoma (p<0.0001), higher in males (p=0.0001) and lower in older patients (p=0.009). Fas, Fasl, and survivin scores were not related to prognosis but the ratio of a Fas to Fasl > or = 1 was related to longer survival (HR=0.72; p=0.02).

None of these markers had predictive value for chemosensitivity at the level of significance 0.01. However, a borderline significant interaction was observed, chemotherapuy being more efficient for Fasl negative (HR=0.69) as compared with Fasl positive (HR=1.03; p=0.06), as well as for Fas:Fasl ratio >1 (HR=0.51) as compared with a ratio of 1 (HR=1.13) or a ratio <1 (HR=0.80; p=0.05).

Conclusion: Two non mitochondrial related apoptotic factors of the death receptor pathway have borderline predictive value (Fasl and Fas/Fasl). The benefit of chemotherapy was observed among Fasl negative patients and those with Fas:Fasl ratio > 1. Current research is ongoing to pool these results with other adjuvant trial populations in order to validate their use in selecting patients for cisplatin-based chemotherapy.