Value of Cyfra 21-1 (C21) as determinant of survival, predictor of disease course and assistant of therapeutic decisions in non-small-cell lung cancer (NSCLC) patients (pts): a large 15-year study.

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To evaluate prognostic usefulness of C21 and, particularly to detect its value as early predictor of treatment results, NSCLC course and to decide neo-adjuvant or adjuvant CT in early stages, serum levels were measured during a 15-year period, in 2348 NSCLC pts and 376 pts with benign lung diseases. In 829 pts with early disease (I-IIIA) submitted to surgery (S), measurements of serum markers were performed immediately before S. Included in this group were 465 pts submitted to surgery alone (S), 276 to S plus adjuvant CT (SCT) and 88 to neo-adjuvant CT (CTS).

In all 1768 pts submitted to chemotherapy (CT) measurements were performed at the start of treatment; in 21.2% after 1st course in 65.5% after 2nd course and in 93.4% at the end of CT. In 798 pts, C21 was regularly monitored thereafter, each 2/3 months during all survival time. Overall more than 16000 C21 measurements were performed.

Median values in benign diseases were significantly lower than in NSCLC pts. Using cut-off value of 3.3 ng/ml with a specificity of 95%, overall sensitivity for NSCLC was 69.2%. The percentage of higher than normal C21 values increase as staging advances (I - 29%; IV - 87%), so there is no place for C21 in early diagnosis.

Baseline levels had a week although significant relationships with response to CT (p=0.049). However % change at the end of 1st and 2nd course of CT were more strongly related to survival and TTP than imaging assessment (p=0.00024 and p=0.0012, respectively).

Significant increases of C21 preceded evidence of disease progression in more than 95 % of NSCLC cases. Marginal (<2%) false-negative results allow us to take earlier therapeutic decision either to change CT treatment, to begin a more efficient 2nd line treatment or even to stop aggressive therapy. Cox’s multivariate analysis identified C21 (among the 25 more frequently factors related to survival) as the strongest independent survival prognostic factor.

Baseline levels above 3.3 ng/ml were related with a poor survival for all, including early stages. Patients with surgical stages but with high C21 values, submitted to S alone, present a disappointing median survival. This means that should be upper-staged and treated accordingly. Adjuvant and particularly neo-adjuvant CT treatment seems mandatory in these cases. In which concerns second-line CT the level of C21 at the beginning of treatment is also strongly related with the results obtained.

The closed monitoring of C21 values allows a quick start of 2nd line CT and the results in terms of response and survival were significantly related to this behaviour.

Cyfra 21-1 is in conclusion, a strong prognostic factor for survival that should be considered a very important tool for staging, therapeutic decision, CT treatment’s evaluation and early detection changes in the course of disease. Thus C21 baseline values should be included in all randomized trials avoiding bias enrolment and allowing a more efficient response evaluation. Significant survival gains can be obtained with the correct usage of this highly specific, easily available and inexpensive method.

Analysis of EGFR gene copy number, EGFR mutations, KRAS mutations and EGFR expression in a cohort of non-small cell lung cancer patients treated with epidermal growth factor tyrosine kinase inhibitors at a North American institution.

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Background: Molecular profiling of tumours for tailored anti-cancer therapy promises improved efficacy, morbidity minimization and optimal use of therapeutic resources by health care providers. The epidermal growth factor (EGFR) tyrosine kinase inhibitors (TKI) Gefitinib (Iressa) and Erlotinib (Tarceva), a new class of targeted agents, are approved for the treatment of advanced non-small cell lung cancer (NSCLC). Unfortunately, only 8-15% of patients show an enhanced response to these drugs. Improved predictors of response and resistance to these agents are needed. It has been suggested that responders are identifiable by increased copy number of, or the presence of activating mutations in, the EGFR gene, whereas those exhibiting primary resistance carry mutually exclusive point mutations in the KRAS gene. We set out to investigate the correlation between clinical outcome and the presence or absence of these molecular markers in a population of patients treated with these agents in our institution.

Methods: Non-small cell lung cancer patients treated with Gefitinib and/or Erlotinib at the Tom Baker Cancer Centre (TBCC) between 2002 and 2006 have been identified and included in the study. After the granting of ethical approval, diagnostic samples were obtained. EGFR protein expression has been performed by standard immunohistochemistry (IHC) techniques. Chromogenic In-Situ Hybridization (CISH - a variant of the FISH technique) is being performed. Genomic DNA is isolated from formalin-fixed paraffin embedded samples and used in a nested PCR reaction to amplify exons of interest. Amplified exons are then directly sequenced using dye-terminator PCR and an Applied Biosystems 3130 genetic analyzer. EGFR gene copy number and presence or absence of mutations/deletions in the EGFR and KRAS genes are then correlated with patient response and outcome.

Results: 65 patients, 45 treated with Gefitinib, 17 with Erlotinib as a first EGFR TKI were included; another 3 patients were treated on the BR-21 protocol (Erlotinib vs. placebo) as a first EGFR TKI and subsequently received Gefitinib after progressing. 40% of diagnostic samples are cytological and provide additional molecular analytical challenges. To date, about a third of cases have been assessed by DNA sequencing: 2 EGFR exon 19 deletions out of 19 samples (5%) and 1 KRAS exon 2 mutation out of 16 samples (6%) have been detected. EGFR IHC analysis and CISH staining are currently underway.

Conclusion: At the TBCC, in a select number of patients with advanced NSCLC, both EGFR TKI’s demonstrated clinical and radiologic anti-tumor activity with minimal side effects. The responders to both drugs at our institution were predominantly female, non-smoking Asians with adenocarcinoma. Detailed molecular analysis of NSCLC continues to pose challenges. The relationship between the presence or absence of these markers to each other and to patient outcome and specific demographic characteristics will be presented.