A CA dinucleotide repeat length polymorphism of the first intron of epidermal growth factor receptor (EGFR) and EGFR alterations in Japanese lung cancers

Okudela, Koji1 Kagayama, Sinji1 Suzuki, Masaya1 Takamochi, Kazuya2 Niwa, Hiroshi2 Ogawa, Hiroshi2 Shimura, Kazuya2 Tsumiya, Hiroshi2 Haruhiko1

1 Hamamatsu University School of Medicine, Hamamatsu, Japan 2 Seiheikai Katsurahara Hosp, Hamamatsu, Japan

Background: The purposes of the present study are to evaluate a possible genetic factor determining sensitivity to EGFR alterations in cases of lung cancers, and also to verify whether such factor can be an indicator predicting molecular targeting drugs responsiveness. A CA dinucleotide repeats polymorphism of the first intron of EGFR has recently been reported to be associated with occurrences of EGFR transcription in lung cancers, and with EGFR inhibitor responsiveness in head and neck cancers. We here examined this polymorphism for both tumor and non-tumor tissues of primary lung cancer cases, and have analyzed correlations of the polymorphism with EGFR alterations Method: A hundred sixty nine lung tumors and corresponding normal parts were subjected to analyses. Locus of first intron of EGFR covering CA-repeat stretch were PCR-amplified by using FAM-labeled primers. CA-repeats lengths were determined by acrylamide-gel electrophoresis with DNA sequencer (SIMAZU DSQ).

Results: We found that the constitutional shorter stretch of this repeats in the subjects was associated with occurrences of EGFR copy number gains (Chi-square test; P = 0.031) in tumors, and that the tumors having shorter stretch were more sensitive to gefitinib treatment (Chi-square test; P = 0.0241).

Conclusions: We conclude that the CA dinucleotide repeat polymorphism can be a genetic factor influencing occurrences of EGFR copy number gains in tumors, and this observation entails the rationale for usage of this polymorphism for application of targeting therapy.

Methods: The pathology, radiologic records, laboratory investigations and medical records of 65 patients treated with the EGFR TKIs Erlotinib or Gefitinib between May 2002 and June 2006 were reviewed. Complete or partial radiologic response (CR, PR), stable and progressive disease (SD, PD) were defined as per RECIST criteria. Partial response in non-measurable radiologic disease was characterized as regression of lymphangitic carcinomatosis. Symptomatic response was defined as decreased shortness of breath or pain, decreased FiO2 or improvement in ECOG performance status.

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. 5 patients treated with Gefitinib as a first EGFR TKI, were later treated with Erlotinib. Baseline characteristics of the 45 patients treated with Gefitinib; 24% Asian, 73% Caucasian; 60% female; 29% life long non-smokers, 42% ex-smokers, 29% smokers; 56% adenocarcinoma, 13% squamous, 2% adenosquamous, 7% large cell, 9% BAC and 13% unknown. 1 patient achieved a CR, 6 (13%) had a PR, 16 (36%) had SD with 22 (49%) showing PD. Clinically, 13 (29%) patients experienced symptomatic improvement, 15 (33%) reported no change, and 17 (38%) patients experienced symptomatic decline. The 7 responders were predominantly non-smoking Asian women with adenocarcinoma. Of the 17 patients treated with Erlotinib as a first EGFR TKI, baseline characteristics were; 24% Asian, 76% Caucasian; 76% female; 41% life long non-smokers, 29.5% ex-smokers, 29.5% smokers; 65% adenocarcinoma, 23% squamous, 6% BAC, and 6% other. 2 (12%) patients had a PR, 7 (41%) had stable disease and the other 8 (47%) patients progressed on treatment. Symptomatically, 7 (41%) patients experienced improvement, 6 (35%) had no change, and 4 (24%) experienced symptom progression. Both responders were female non-smokers with adenocarcinoma, however one was Asian, the other Caucasian.

Conclusions: 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. Our experience in a Canadian setting supports the impression that this constellation of clinical characteristics is a useful, though not specific, predictor of response to these agents.

Erlotinib monotherapy for stage IIIIB/IV non-small cell lung cancer: A prospective study by the Korean Cancer Study Group(KCSG)

Park, Byeong-Bae1 Ahn, Myung-Ju2 Kim, Sang We1 Kim, Heung-Tae1 Lee, Jong Seog2 Kang, Jin Hyung3 Cho, Jae Yong4 Song, Hong Suk5 Sohn, Chang Hak6 Park, Keunchil7

1 Hanyang University College of Medicine, Seoul, Korea 2 Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea 3 Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea 4 Research Institute and Hospital, National Cancer Center, Seoul, Korea 5 Seoul National University Bundang Hospital, Seongnam, Korea 6 Kang Nam St. Mary’s Hospital, The Catholic University of Korea, Seoul, Korea 7 Yonsei University College of Medicine, Yongdong Severance Hospital, Seoul, Korea 8 Keimyung University School of Medicine, Daegu, Korea 9 Inje University College of Medicine, Busan, Korea