R497K ARE ASSOCIATED WITH PFS AND OS TO EGFR TKIS IN NSCLC PATIENT

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It has been well known that EGFR mutation on particular exons is a strong predictive biomarker to EGFR TKIs in NSCLC pts. However, some pts having wild type EGFR do not infrequently show clinically favorable outcome to EGFR TKIs. Accordingly, we hypothesized that clinical outcome and skin toxicity to EGFR TKI might be related to specific single nucleotide polymorphisms regulating the expression of EGFR gene. In 211 advanced or metastatic NSCLC pts receiving gefitinib or erlotinib, we assayed mutation status of EGFR in paraffin embedded tumor tissue using direct sequencing and genotyped six different SNPs in genomic DNA extracted from peripheral blood. Sex ratio was 106:105 and median age was 63.2 (35.0-82.0). Histological subtype was adenocarcinoma 175, squamous cell ca. 32, and large cell ca. 3, etc. Objective response was observed in 78pts (36.9%) and SD in 69pts (32.7%). Median PFS and OS was 8.7 + 11.3 and 15.9 + 14.8 months, respectively. Analysis for EGFR mutation was done in 167pts and 68 (40.7%) showed EGFR harboring sensitive mutation. In R497K, RR type was 35 (21.0%) and RK and KK type were 132 (79.0%). In D994D, GG type was 76 (45.5%) and GA and AA types were 91(54.5%). Statistically significant differences of PFS and OS were observed between wild and hetero-/homozygote variants of R497K (p = 0.037 and p = 0.054, respectively) in the pts harboring mutant type EGFR. But, in the pts harboring wild type EGFR, GA+ AA genotype of D994D was observed much longer PFS and OS compared with GG genotype (p = 0.013 and p = 0.035, respectively). In the pts harboring adenocarcinoma and wild type EGFR, disease control was associated with GG genotype compared with GA+ AA genotype of 2607G > A in exon 20 (p = 0.051). We suggest that R497K and D994D, germline genetic variations of EGFR gene, might be useful pharmacogenetic biomarker to predict longer PFS and OS in NSCLC pts harboring mutant type and wild type EGFR, respectively.