Lung cancer, specifically NSCLC, is a major cause of cancer related death all over the world. Personalized cancer therapy, utilizing either germline pharmacogenomic or somatic mutation analyses, can increase therapeutic success and improve outcomes in lung cancer patients. To date, few integrated studies of germline pharmacogenomics and somatic mutations in cancer patients have been undertaken. The long-term aim of the study is to determine whether the identification of both somatic mutation and germline variation that govern pharmacodynamic and pharmacokinetic responses to cancer chemotherapy can be used concurrently to achieve better patient outcomes.

We utilized the molecular and clinical data for 404 lung adenocarcinoma patient samples found in The Cancer Genome Atlas (TCGA). Statistical analysis was performed using Kaplan-Meier curves with the Wilcoxon test for overall survival. We identified patients with well-known mutations that affect NSCLC. We further divided these patients based on the presence or absence of variation in any of 6 CYP450 genes (CYP-1A2, 2D6, 3A4, 2C19, 2C9 and 3A5) to identify a possible correlation that can be associated with increased survival.

Analysis revealed a statistically significant survival benefit (n=326, p= 0.029) for the patient population not carrying CYP450 variants compared to the group expressing CYP450 variants.
Analysis on the most common genes targeted in lung cancer (EGFR, ROS1, ALK and MET) uncovered a similar survival advantage (n=323, p=0.029) for the population without CYP450 variants. Further analysis by stage indicated that a survival benefit is associated with the absence of CYP450 variants in stage I patients; patients with advanced stage disease (stage II and III) did not show a similar correlation but did show the same trend.

Our results suggest for the first time a correlation between a patient’s pharmacokinetic handling of cancer drugs, as determined, in part, by genetic variability, and somatic driver mutations. A caveat to our approach using the TCGA is that germline data are not available and one would have to assume that the CYP450 variants in each tumor represent the germline and not de novo somatic mutations. Further retrospective and prospective clinical studies will be needed to evaluate the above conclusions.

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