Serum glutathione peroxidase 3 as a biomarker of postoperative relapse in patients with lung cancer

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Background: Glutathione peroxidase 3 (GPx3) which is an extracellular secretory protein is down regulated in patients with early stage lung cancer. We examined the usefulness of serum GPx3 as a biomarker for monitoring of relapse after surgery.

Methods: We prospectively collected serial serum samples at baseline, 3 months (3m), 6 months (6m), and 12 months (12m) after operation from the patients who underwent surgery during the year 2013. GPx3 levels were measured three times per sample using the enzyme-linked immunosorbent assay, and the mean values were analyzed by t-test and paired t-test.

Results: A total of 170 (100 adenocarcinoma, 41 squamous cell carcinoma, 29 others) patients were analyzed in this study. Mean age was 64.1 years old (range, 39-80) and 27 (15.9%) out of 165 lung cancer patients were confirmed relapse during the median follow-up period of 597.5 days (range, 5-938). The mean GPx3 value at postoperative 6m was significantly elevated in relapsed group than control group (7.90 ± 2.44 μg/mL vs. 6.99 ± 1.79 μg/mL, p=0.047). The mean GPx3 differences were significantly higher in relapsed group than control group at 3m (-0.38 ± 0.39 μg/mL vs. -0.21 ± 0.36 μg/mL, p=0.044), 6m (-0.37 ± 0.42 μg/mL vs. -0.19 ± 0.30 μg/mL, p=0.024), and 12m (-0.38 ± 0.42 μg/mL vs. -0.19 ± 0.28 μg/mL, p=0.012). The mean time to relapse was significantly shorter in high level of GPx3 group at postoperative 3m (694.83 ± 31.86 days vs. 839.05 ± 24.31 days, p=0.007). The mean time to relapse was significantly shorter in high GPx3 difference group between baseline and postoperative 3m (729.76 ± 34.89 days vs. 838.18 ± 24.03 days, p=0.002).

Conclusion: Serum mean GPx3 value at postoperative 6m and the mean GPx3 difference were significantly elevated in relapsed lung cancer. The mean time to relapse was significantly shorter in high level of GPx3 group at postoperative 3m. More large scaled validation studies are warranted.

The biological impact of e-cigarettes on airway epithelial cell transformation and gene expression

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Because the electronic cigarette (ECIG) is designed to deliver nicotine without combusting tobacco, they are widely advertised as a safer alternative to tobacco cigarettes (TCIGs). ECIGs are controversial due to the lack of quality control standards and the paucity of data on their safety and long-term health effects. The absence of product standards and regulation, leading to variability in product quality is a major concern. Studies analyzing the contents of the ECIG cartridge and/or vapor have revealed the presence of major tobacco-specific nitrosamines, volatile organic compounds, and metals. Multiple studies have detected inconsistent levels of nicotine in cartridges and refills between ECIG manufacturers compared to the content labeling. For this reason, each component of ECIGs is the subject of public health and safety concern. In this study, we assess the impact of ECIG exposure on the carcinogenic potential of immortalized human bronchial epithelial cells on a background of silenced p53 and activated KRAS, mutations often observed in the airway of current and former smokers at risk for lung cancer. Our preliminary results demonstrate that exposure to clinically relevant concentrations of ECIG vapor-conditioned media enhance the cancer-associated behavior of ‘at-risk’ airways with a demonstrated capacity for malignant transformation. We observed enhanced colony growth in anchorage independent assays and increased cell invasion-associated morphological changes in three-dimensional air-liquid interface models. In addition, we found that mutant epithelial cells exposed to ECIG vapor-conditioned media induces airway gene expression changes that are similar to those seen with TCIG exposure. Currently, we are defining an ECIG exposure signature. In addition, we will also evaluate the effects of chemical substances present in ECIGs such as tobacco-specific nitrosamines. These studies will identify the potential impact of ECIGs on airway epithelium carcinogenesis and add to our overall understanding of early disease pathogenesis in human lung cancer. These studies were supported by funding from the following: NIH/NCI #U01CA152751 (SMD, TCW), NCI #U01CA152751-51 (SMD, TCW, SJP), NCI #U01CA152751-AS (SMD, KK), NCI #T32-CA009120-36 (SMD, SJP, PCP),
Long-term treatment with dexamethasone induces senescence and progressive loss of proliferation potential in lung adenocarcinoma cells expressing high levels of the glucocorticoid receptor

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We have previously demonstrated that in non-squamous non-small cell lung cancer (nsNSCLC) cells expressing relatively high levels of the glucocorticoid receptor (GR), dexamethasone (Dex) induces reversible G1 arrest that is virtually complete by 72h of Dex treatment. We have also shown that this effect of Dex protects the cells from the cytotoxicity of pemetrexed, a mainstay chemotherapy in advanced nsNSCLC that entails co-administration of Dex. Further, induction of G1 arrest by Dex was confirmed by FLT-PET imaging of tumor lesions in patients treated with Dex for 24h. Here we report the effects of long-term treatment of nsNSCLC cells with Dex. The nsNSCLC cell line models included A549 (GRhi), H292 (GRhi), H1650 (GRlo) and H1299 (GRlo) cells as well as clonal recombinant H1299 cells overexpressing GR. In only the GRhi cells, Dex caused an increase in p21 peaking on Day 7 and declining by Day 14. The cells retained proliferation potential on Day 3 as measured by colony formation. By Day 7 of Dex treatment, the GRhi cells but not the GRlo cells exhibited a senescence phenotype, marked by cytosolic beta-galactosidase activity and increases in p16 and p15 at the mRNA and protein levels as well as significant increases in cell size. The GRhi cells displayed a progressively decreasing ability to form colonies until 6 weeks of Dex treatment. The extent of this loss of proliferation potential was related to relative GR expression levels among the Dex-sensitive cells. When mice bearing xenografts of H1299 (GRlo) or isogenic recombinant H1299-GR (GRhi) cells were implanted with slow release Dex pellets, tumor growth was inhibited only in the H1299-GR cells. Evaluation of a tissue microarray as well as a cDNA array from clinical nsNSCLC tumors showed that about 20 percent of the tumors showed uniform expression of GR that were comparable to the levels required for Dex to induce senescence in vitro or to inhibit tumor growth in vivo. The results suggest that long-term administration of Dex could serve as an additional treatment option for a small cohort of lung adenocarcinoma patients that harbor uniform high levels of GR in their tumor lesions.

Phase I/II trial of X-396, a novel anaplastic lymphoma kinase (ALK) inhibitor, in patients with ALK+ non-small cell lung cancer (NSCLC)

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Background: X-396 is a novel, potent anaplastic lymphoma kinase (ALK) small molecule tyrosine kinase inhibitor (TKI) with additional activity against MET, ABL, Axl, EPHA2, LTK, ROS1 and SLK. It has demonstrated significant anti-tumor activity in both ALK TKI-naive and crizotinib-resistant models of ALK fusion-positive NSCLC.

Methods: In this multicenter phase I/II study, patients (pts) with advanced solid tumors were enrolled in the phase I dose escalation portion of the study and given X-396 on a continuous 28-day schedule (NCT01625234). Doses from 25 up to 250 mg once daily were evaluated and 225 mg was selected for further evaluation in the phase II expansion. Patients in this phase were required to have ALK+ NSCLC and measurable disease. Cohorts included pts who were 1) ALK TKI-naïve, 2) pts who progressed on prior crizotinib and had not received a 2nd generation ALK TKI, 3) pts who progressed on a 2nd generation ALK TKI (may also have received crizotinib), 4) pts with central nervous system (CNS) metastases, and 5) pts with leptomeningeal disease. All pts were assessed for adverse events (AEs) using CTCAE version 4.03, response to therapy was assessed using RECIST 1.1.

Results: As of the October 15, 2015 data cutoff, 53 pts (29 men, 24 women) have been enrolled. Median age is 56 (20-79) years, the majority of patients had ECOG performance status 1 (68%). The most common drug-related AEs included rash (47%), nausea (28%).