Combining Genome Change Index (GCI) and liquid biopsy to predict and monitor therapeutic responses.

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Abstract Disclosures

Background:
Genomic instability of tumor cells has been associated with a poor prognosis. However, impaired DNA repair pathways leading to genomic instability are also described to increase tumor sensitivity to DNA damaging agents. A comprehensive Genomic Change Index (GCI) as an indicator of defective DNA repair is proposed as a potential predictor of cytotoxic chemotherapy (chemo) response. Cell-free tumor DNA (cftDNA) has the potential to provide minimally invasive patient specific biomarkers to monitor tumor burden (liquid biopsy).

Methods:
18 patients (pts) with advanced esophageal cancer (EC; n = 1), pancreatic ductal adenocarcinomas (PDAC; n = 4), small cell (SCLC; n = 6) and non-small cell lung cancer (NSCLC; n = 7) were included. The chemo regimen for PDAC was gemcitabine & nab-paclitaxel. All other pts received carboplatin/cisplatin, with etoposide (SCLC), etoposide, pemetrexed, or paclitaxel (NSCLC; EC). Chemo-resistant cancers (R) were defined as having progressive disease (PD), chemo-sensitive cancers (S) as stable disease (SD) or partial response (PR) on initial therapy. DNA was extracted either from tumor tissue or pre-treatment plasma samples. Copy-numbers were called from shallow shotgun sequencing (~2.5x10^7 reads, Illumina) in genomic windows of 500kbp and converted into a score based on Gaussian transformations. Somatic mutations were called from targeted sequencing and quantified in follow-up plasma DNA by digital PCR.

Results:
Significantly lower GCI were detected in R vs. S (p = 0.03). Liquid biopsies were obtained for 6 patients with PD, SD, or PR. Decreasing cftDNA levels were detected as early as 2h after starting the first cycle in a pt who received 6 cycles of chemo showing SD. In the one EC pt (PR) < 6 cftDNA copies/mL plasma were detected at end of treatment. Rising cftDNA concentration were detected in 3 PD pts. One NSCLC pt (PD) showed a slight cftDNA decrease from baseline to cycle 2 with still very high concentrations ( > 1000 cp/mL plasma).

**Conclusions:**
As shown for other cancers, GCI may serve as predictor of therapy response to DNA-damaging chemo for the investigated cancer types. Liquid biopsy with cftDNA is a highly specific, sensitive and rapid surveillance biomarker.