4506   **Oral Abstract Session**

Cell-free DNA methylation as a predictive biomarker of response to neoadjuvant chemotherapy for patients with muscle-invasive bladder cancer in SWOG S1314.

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Background: Neoadjuvant chemotherapy is the standard of care in muscle-invasive bladder cancer patients. However, treatment is intense, the overall benefit is small, and there is no established marker to identify patients who benefit most. The aim of the study is to characterize cell-free DNA (cfDNA) methylation from patients receiving neoadjuvant chemotherapy in SWOG S1314, a prospective cooperative group trial, and to correlate the methylation signatures with pathologic response. **Methods:** Blood samples were collected prospectively from 73 patients before and during standard neoadjuvant chemotherapy. At radical cystectomy, pathologic response was documented. Plasma cfDNA was profiled using Infinium MethylationEPIC BeadChip array. Differential methylation between pathologic responders (≤pT1N0M0) and non-responders was analyzed, and a Random Forest model was used to generate a classifier predictive of treatment response. **Results:** Using pre-chemotherapy plasma cfDNA, we developed a methylation-based response score (mR-score) predictive of pathologic response. The mR-score also could be calculated using plasma samples collected after the first cycle of neoadjuvant chemotherapy, resulting in a similar predictive ability. Furthermore, we used cfDNA methylation data to calculate the circulating bladder DNA fraction, which had a modest but independent predictive ability for treatment response. When we combined the mR-score and circulating bladder DNA fraction, we successfully predicted pathologic response outcomes in 79% of patients based on their plasma collected before chemotherapy and after 1 cycle of chemotherapy. **Conclusions:** Our study provides proof of concept that cfDNA methylation may be used to predict treatment response in bladder cancer patients receiving neoadjuvant chemotherapy. Clinical trial information: NCT02177695. Research Sponsor: U.S. National Institutes of Health, Conquer Cancer Foundation of the American Society of Clinical Oncology, Other Foundation, Tower Cancer Research Foundation.