A Study to Evaluate the Prognostic and Predictive Utility of CCP and HRD Assays and Genetic Sequencing in Patients undergoing Neoadjuvant Chemotherapy in Bladder Cancer

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BACKGROUND
Clinical trial data have shown a survival advantage associated with the use of cisplatin-combination neoadjuvant chemotherapy (NACT) in muscle invasive urothelial bladder cancer (UBC). Selecting patients that are likely to respond and benefit is a concern when counseling patients for NACT.

OBJECTIVES
In an effort to identify potential biomarkers in UBC that will aid in characterizing disease aggressiveness and/or predict cisplatin chemo-sensitivity, we explored the utility of a combination of nucleic acid-based assays.

Specific aims include:
1. To evaluate the prognostic and predictive utility of cell cycle progression (CCP) and/or homologous recombination deficiency (HRD) score in patients with cT2-4aNx TCC cancer of the bladder who were treated with radical cystectomy.
2. To evaluate a set of 42 candidate genes that have been recently characterized as important drivers of bladder cancer development and may also have clinical utility.

METHODS
Between 2003 and 2014 formalin-fixed paraffin-embedded bladder tumor from line of TURBT was obtained from patients before treatment with NACT.

All patients had muscle invasive UBC and underwent radical cystectomy. Molecular assays included the CCP score, the HRD score, and genetic sequencing of a set of genes recently implicated as potential drivers in UBC.

CCP and HRD scores and gene mutations were correlated to complete pathologic response (pCR) and disease recurrence.

RESULTS
A total of 90 samples were obtained from patients who underwent NACT followed by cystectomy. Eighty-eight patient samples had adequate tissue for assay, of which 70 samples were able to yield both CCP and HRD scores.

Higher CCP and HRD scores were associated with pCR on univariate analysis (OR 2.39, CI 1.15-4.95, p=0.011 and OR 2.10, CI 1.04-4.22, p=0.033, respectively), but not when adjusting for each other, indicating that CCP and HRD do not provide significant independent predictive information.

An HRD score greater than 30 (4th quartile) was associated with a decreased risk of recurrence, and remained predictive of decreased recurrence when accounting for pCR (p=0.019).

Among 82 genes sequenced, mutations identified in RB1 and TP53 genes were associated with pCR (p=0.0040 and p=0.030, respectively). Best multivariable models for pCR were either RB1 and CCP (OR 3.70, CI 1.14-12.1, p=0.028 and OR 2.50, CI 0.93-6.74, p=0.053, respectively); or RB1 and HRD (OR 4.24, CI 1.01-17.2, p=0.0432 and OR 2.50, CI 0.93-6.74, p=0.053, respectively). Best multivariable models for pCR were either RB1 and CCP (OR 3.70, CI 1.14-12.1, p=0.028 and OR 2.50, CI 0.93-6.74, p=0.053, respectively); or RB1 and HRD (OR 4.24, CI 1.01-17.2, p=0.0432 and OR 2.50, CI 0.93-6.74, p=0.053, respectively).

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CONCLUSION
RB1 mutations are associated with response to cisplatin NACT in UBC patients. The predictive ability appears to be improved by the addition of either CCP or HRD scores. If validated, these tests could be used to help identify chemo-responsive patients.

In addition, HRD could be used to predict risk of recurrence in patients after NACT followed by cystectomy.

REFERENCES
1. Jacobs BL et al. CA Cancer J Clin. 2010;60:244-72

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