Editorial

A new subtyping model for residual invasive disease after cisplatin-based neoadjuvant chemotherapy for muscle invasive bladder cancer

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Muscle invasive bladder cancer (MIBC) is an aggressive malignancy and half of the patients develop metastatic disease within 2 years, which is generally incurable and leads to early mortality (1). Based on prospective randomized trials, MIBC is treated with cisplatin-based neoadjuvant chemotherapy (NAC) followed by radical cystectomy (RC) (2-4). However, when examining the SWOG8710 trial that evaluated optimal MVAC (methotrexate, vinblastine, doxorubicin, cisplatin) NAC, the 5-year overall survival (OS) exhibited a modest absolute increment from 42% to 57% with RC alone to NAC followed by RC. Those without pathologic complete remissions (> pT0) demonstrated poor outcomes with a median survival of 3.7 years, while those with pT0 disease at RC exhibited essentially a normal life expectancy (5). Hence, it is critical to understand the drivers of resistance in those with > pT0 disease following NAC in order to make further advances in these patients.

The Cancer Genome Atlas (TCGA) and other groups have reported molecular subtypes based on gene expression of untreated MIBC patients (6,7). The authors took a positive step in this direction following their previous publication where they evaluated the association of intrinsic subtypes (basal, luminal, luminal-infiltrated, and claudin-low) of MIBC based on gene expression of baseline tumor employing the GenomeDx platform with response to NAC (8). In this retrospective analysis, they were able to demonstrate that basal subtype tumors showed the most improvement in OS with NAC, while luminal tumors had the best OS with and without NAC. Luminal-infiltrated and claudin-low tumors displayed low OS and were presumed to likely benefit from newer targeted agents.

In this new publication (9), the authors studied residual muscle-invasive disease after cisplatin-based NAC from 133 patients of whom 116 had matched pre-NAC samples. They report that established molecular subtyping models proved to be inconsistent in their classification of the post-NAC samples. They used unsupervised consensus clustering and classified the tumors into four distinct consensus clusters (CC), namely, CC1-Basal, CC2-Luminal, CC3-Immune and CC4-Scar-like. They note that the CC1-Basal and CC2-Luminal subtypes resembled the pretreatment subtypes. They identify a new CC3-Immune subtype that lacked both basal and luminal markers. This subtype has higher T cell infiltration and higher expression of immune associated genes, most remarkably, programmed death ligand 1 (PD-L1) and cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4). They also identify a novel CC4-Scar-like subtype with increased expression of p-53 like signature as described in the MD Anderson classifier (10). They note that the CC4 subtype had significantly better OS as compared to CC3 and CC2 on multivariable analysis.

Approximately 42% of tumors remained retained their subtype after chemotherapy. Among the remaining, a loss of luminal and basal marker expression coupled with an

enrichment for immune infiltration (CC3-Immune occurred in 34% of cases). The CC3-Immune subtype evolved from all pre-NAC subtypes, suggesting a more generalized immune response associated with chemotherapy-induced cell death. Luminal tumors were more likely than basal tumors to become CC4scar-like after NAC. They hypothesize that the shift in subtypes after NAC is either due to tumor plasticity or tumor heterogeneity leading to selection of chemotherapy resistant tumor cell clones. The retrospective nature of the analysis and the modest sample size are limitations. Therefore, this classification will need to be validated prospectively in larger datasets. Furthermore, the functional importance of these subtypes to select therapeutic regimens in the adjuvant setting requires study. The authors note that this data was collected from patients before the introduction of checkpoint inhibitors. It is unclear if the subtype classification after neoadjuvant chemotherapy is just a reflection of chemotherapy induced cell damage and transient selection of resistant clones or is a true representation of the evolving pathology. Molecular analyses at the single cell level will shed greater insights (11). Genomic alterations vary based on gene expression subtypes in untreated MIBC, and this needs to be examined in post-NAC tumor too (12). In this context, a study of matched primary and metastatic tumors demonstrated that chemotherapy-treated urothelial carcinoma is characterized by intrapatient mutational heterogeneity and the majority of mutations are not shared (13). In addition, the authors of this study demonstrated that both branching evolution and metastatic spread are early events with clonal mutations involving L1 cell adhesion molecule (L1CAM), integrin signaling pathways and APOBEC induced mutagenesis following chemotherapy. Another study evaluated baseline and post NAC tumor with whole exome sequencing and demonstrated no overall increase in tumor mutational burden post-chemotherapy although post-treatment tumor heterogeneity predicted worse OS (14). Furthermore, alterations in cell-cycle and immune checkpoint regulation genes were observed in post-treatment tumors.

Therefore, a lot of work needs to be done to translate these data for use in the clinic. Currently patients with or without pathologic complete response following neoadjuvant chemotherapy for MIBC after cystectomy are observed and are treated with chemotherapy or immune checkpoint inhibition on recurrence of disease. Moreover, whether the subtype information obtained after RC following NAC will correspond to the molecular profile of microscopic metastatic tumor cells is unclear. Presumably, temporal separation of macroscopic metastases from RC may impact on the molecular profile of metastatic tumor. Does it make more sense to obtain a fresh biopsy of metastatic tumor after diagnosis of metastatic malignancy to guide treatment based on the pathology and molecular signature at that time?

Another use of the classification could be in the adjuvant setting. The current standard of care in the adjuvant setting following NAC is observation. Currently, 3 trials are ongoing to identify the efficacy of atezolizumab (NCT02450331), nivolumab (NCT02632409) or pembrolizumab (NCT03244384) in the adjuvant setting of high-risk MIBC (15). It will be interesting to see if the current subtype classification of MIBC following NAC predicts benefit with programmed cell death 1 (PD-1)/PD-L1 inhibitors in the adjuvant setting of MIBC. However, it is unclear if subtype classification will be superior to or complement other potential biomarkers of immunotherapy response such as PD-L1 expression, tumor mutation burden (TMB), etc. Phase III trials of neoadjuvant chemotherapy combined with checkpoint inhibitors have been recently launched (e.g., NCT03661320), which will afford an opportunity to interrogate the molecular biology of residual tumors after these combinations.

In conclusion, the paper advances our knowledge of the molecular biology of residual muscle-invasive disease after cisplatin-based NAC Four distinct CC are proposed: CC1-Basal, CC2-Luminal, CC3-Immune and CC4-Scar-like subtypes. The data needs to be validated prospectively in larger datasets with attention to functional and therapeutic relevance. Additionally, study of post-therapy metastatic tumor tissue using biopsies as well as rapid autopsy tissue will complement knowledge gained from study of post-NAC tumor (16,17).

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Footnote

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