Editorial

Can post-neoadjuvant therapy molecular classification guide future treatment selection for muscle-invasive bladder cancer?

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While platinum based chemotherapy has been the backbone of systemic therapy for muscle invasive bladder cancer for decades, little is known about how this treatment changes the tumor phenotype, or if subsequent management decisions should be based on those changes. Seiler *et al.* present interesting data on clustering and classification of post-chemotherapy tumors. Their data support their model that chemotherapy is not simply selecting out resistant subclones but it is also inducing changes that may promote resistance and potentially vulnerabilities for subsequent therapy.

Multiple groups have developed molecular classifications of treatment-naïve muscle invasive bladder cancers with the hope that their application to pre-treatment tumors may identify a pattern of sensitivity to guide care (1-5). At the basic level, separation of tumors into basal or luminal subtypes suggest that basal tumors may benefit the most from neoadjuvant chemotherapy (NAC), based on improved survival (but not pathologic response) (6,7). To enable implementation of this classification scheme, Seiler previously developed a single-patient classifier based on four subtypes (luminal, basal, claudin low and luminal infiltrated) (7). Yet the application of this pre-chemotherapy subtyping has not been adopted, and the intrinsic plasticity of subtypes remains controversial.

In a follow-up manuscript, Seiler applied clustering and classification to 116 matched tumors "resistant" to chemotherapy (8). While 42% of tumors remained the same subtype after NAC, 34% of tumors were in an immune infiltrated cluster (called CC3) and 12% were scar-like (called CC4). Luminal tumors were more likely to become scar-like than basal tumors (12/55 *vs.* 2/61, P=0.006). The CC3 immune cluster, which expresses neither luminal nor basal markers, appears to be a new subtype not seen prior to chemotherapy, with expression of immune exhaustion markers (CTLA4, MPEG1 and CD27). It appears instead that the cluster is driven by loss of differentiation markers, presumably driven by response to chemotherapy, as much as infiltrating immune cells. It is not clear if the scar-like phenotype (CC4) represents an intrinsic tumor cell phenotype or simply the phenotype of the stromal response in the setting of sensitive, though not eradicated, tumor. The authors separately analyzed scar tissue from patients with a pathologic complete response, and its expression profile is very similar to that of CC4.

Similar to the molecular subtypes of chemotherapy naïve tumors, these post-chemotherapy subtype clusters raise further questions about the instability and heterogeneity of MIBC subtypes. In particular, the immune CC3 expresses inhibitory immune genes, suggesting they might enrich for the ~20% of tumors that respond to checkpoint inhibitors. Moreover, their model suggests chemotherapy induces immune cell infiltration and an immune-responsive phenotype, perhaps converting immune depleted tumors to inflamed. It is not clear from the clinical data that prior

chemotherapy enhances immune responses (9-12).

How these observations affect clinical practice remains to be seen. To contribute to management decisions in the clinic, data regarding the post-treatment consensus clusters and subsequent therapy response is needed. To be fully integrated into clinical management decisions, there is the need to develop single sample subtype classifiers, as the authors did with treatment-naïve tissue. These classifiers will be adopted only after validation from trials evaluating treatment response prospectively guided by subtype classification. Moreover, with the recent report of significant responses to neoadjuvant immunotherapy (13), there is great opportunity to develop better multitargeted combination strategies to maximize benefits for muscle invasive bladder cancer patients.

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Footnote

Conflicts of Interest: JJ Meeks—Consultant: Merck, AstraZeneca, Ferring, Cold Genesys, Janssen; Research Funding: Abbvie, Tesaro, Epizyme; Compensation for talks: AUA, OncLive; Clinical Trials: SWOG, Genentech, Merck, AstraZeneca. M Hussain—Research support through contracts with Northwestern University: Genentech, AstraZeneca, Bayer; Honorarium: AstraZeneca, Pfizer, Sanofi Genzyme; Travel support: Pfizer, Sanofi Genzyme, Genentech. DJ VanderWeele has no conflicts of interest to declare.

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