



Understanding chemotherapy-induced changes in bladder cancer biology: a necessary step towards tailored treatment in cisplatin-refractory disease

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Despite undeniable scientific progress, our growing understanding of the complex biology of bladder cancer still fails to translate into widely-available options for treatment personalization in this frequent disease. The now decades-old cisplatin-based chemotherapy remains the only gold standard for untreated disease at both the localized and metastatic stages. In muscle-invasive bladder cancer (MIBC), pathological response to cisplatin-based neoadjuvant chemotherapy (NAC) dichotomizes the patients into ~40% responders and ~60% non-responders, with dramatically decreased recurrence-free survival and overall survival in the latter (1). Thus, in recent years, while several teams and consortiums have published large-scale molecular characterization of untreated MIBC (2-5), they have also made notable efforts to describe the respective chemosensitivity of the various clusters and subtypes of bladder cancer. However, clinicians still lack to this day the routine molecular tools needed to identify the patients who will indeed benefit from NAC.

A notable effort in this field has been previously reported by the team of Seiler *et al.* in 2017 (6). Based on two large cohorts of patients, respectively treated with NAC and radical cystectomy (RC) or RC alone, they described the natural history of the various subtypes of treatment-naïve MIBC, defined by both a custom-made genomic subtype classifier (GSC) and the molecular classifications of Lund (2), The Cancer Genome Atlas (TCGA) (3), the

MD Anderson Cancer Center (4) and the University of North Carolina (5). They demonstrated that patients with a consensual transcriptomic subtype of “basal” MIBC, accurately identified by their own GSC, derived the most benefit from NAC, showing a better prognosis in the NAC+RC cohort than the RC cohort, as opposed to the other tumor subtypes. This was not associated with an increased rate of pathological major response, which retained an independent prognostic value. To the clinician, the awaited validation and routine availability of tools such as their GSC offers the perspective of better patient selection for NAC.

In a subsequent article recently published in *Cancer Research* (7), Seiler *et al.* chose to describe the transcriptomic landscape of cisplatin-resistant bladder cancer, using a cohort 133 patients with residual disease after cisplatin-based NAC. Focusing on this particular clinical situation is highly relevant, since the persistence of disease after NAC most often heralds disease recurrence and, ultimately, patient's death. Better comprehension of the native biology of cisplatin-resistant MIBC as well as its possible transformations on chemotherapy could offer new leads for novel neoadjuvant or adjuvant treatments.

First, by applying both their GSC and the four above-cited classifications, Seiler *et al.* observed that the transcriptomic profiles of matched pre- and post-NAC samples often differed. This demonstration of

temporal heterogeneity evidences either the selection of chemoresistant subclones or the direct impact of chemotherapy on transcription; the prognostic significance of this “subtype switch”, however, remains unclear. If applied to the development of adjuvant strategies, this clearly illustrates the necessity of using current rather than previous tumor samples in both patient selection and subgroup analyses. An important question, unassessed in this paper, is whether the tumor profile would revert to its original subtype when relieved from treatment pressure; this is of critical importance in tailoring personalized first-line treatments in patients with disease recurrence based on the previous characteristics of the localized tumor, so as to avoid re-biopsy.

Paradoxically, when the previous paper by Seiler *et al.* showed that basal tumors derived the most benefit from NAC (6), the frequent discrepancies between the transcriptomic profiles of pre- and post-NAC samples in this new report were mostly due to frequent shifts from initially luminal to ultimately basal tumors. The fact that basal tumors seem to dominate the transcriptomic landscape of cisplatin-resistant MIBC may be something to consider in the designing of adjuvant treatments.

However, an important lesson learned from this report is that the application of molecular classifications designed for treatment-naïve disease to chemotherapy-treated disease may not turn out to be the most pertinent approach. Indeed, by performing anew the unsupervised clustering of post-chemotherapy samples, the authors identified four transcriptomic consensus clusters (CC) in cisplatin-resistant MIBC: if two of them were found to be redundant with their basal and luminal subtypes of treatment-naïve MIBC (CC1-basal and CC2-luminal, respectively), they described two novel CC3 and CC4 clusters specific to chemotherapy-treated disease.

The novel CC4-scar-like subtype was defined by high expression of wound-healing genes and epithelial-to-mesenchymal transition (EMT) genes, similar to that of the cicatricial tissue of the tumor bed in complete responders. This scar-like subtype, originating mostly from initially luminal tumors, was found to be enriched in pathological partial responders and associated with a favorable prognosis reminiscent of that of complete responders. Intuitively, identifying these “almost responder” patients could allow for the withholding of adjuvant treatments, with potential benefit for both the patient himself and the statistical efficiency of future trials evaluating these treatments.

Finally, a CC3-immune subtype lacking both the

basal or luminal transcriptomic signatures was defined by high immune infiltration, high T-cell and T-helper signatures and high immune checkpoint expression. Loss of basal/luminal differentiation concurrent with immune infiltration was possible for both initially luminal and basal tumors. The CC3-immune subtype shared its immune characteristics with the CC1-basal subtype, making these two tumor subtypes the ideal candidates for adjuvant checkpoint blockade in cisplatin-resistant MIBC, of which they represent more than 50% in the paper by Seiler *et al.* This therapeutic strategy is already being evaluated in phase III trials (8), and transcriptomics correlates of clinical benefit inspired by the work of Seiler *et al.* should be of great interest.

The potential applications of this work to the prognostic assessment of cisplatin-resistant MIBC and the selection of patients for adjuvant therapy after the failure of NAC are important. It is also quite tempting to extrapolate these findings to the advanced setting, especially the appearance of immune infiltration on chemotherapy. Indeed, this raises questions regarding the current development of potential biomarkers of sensitivity to PD-(L)1 inhibitors in advanced urothelial carcinoma (UC). In prospective trials, the search for molecular correlates of clinical benefit from immunotherapy in cisplatin-pretreated patients has mostly resorted to previous fixed samples (9,10), and since routine practice does not require re-biopsy in case of chemotherapy failure, the available samples used in these studies may have mostly been obtained before previous exposure to chemotherapy, at either the MIBC or metastatic stage. Thus, an impact of chemotherapy on the molecular and immunological properties of the advanced tumor, similar to that observed in MIBC, may have been overlooked. This could have grievous consequences so as to the intelligibility of data regarding any association between transcriptomic tumor subtypes and benefit from immunotherapy. For instance, in the 2016 much-cited phase II study by Rosenberg *et al.* describing the efficacy of the anti-PD-L1 antibody atezolizumab in chemotherapy-pretreated advanced UC, this drug was found to be most effective in TCGA cluster II tumors (9). Although we admit that the biology of MIBC and advanced UC may be different, we note that in the 2018 study by Seiler *et al.*, the pre-NAC TCGA clusters in MIBC were found to be changeable after NAC (7). This may also be the case in advanced disease after first-line chemotherapy, shedding doubts as to their reliability as biomarkers. However, it is interesting to note, first, that the reputedly immunotherapy-responsive pre-

NAC TCGA cluster II tumors comprised all GSC-defined “infiltrated luminal” and part of the “basal” tumors, second, that “infiltrated luminal” tumors often turned into CC3-immune tumors after NAC and, third, that most “basal” tumors turned either into CC3-immune or the equally infiltrated CC1-basal tumors. Although very indirectly, this suggests that chemotherapy may contribute to create an immunotherapy-responsive microenvironment in cluster II tumors, partially explaining its better efficacy in this subtype.

Finally, it will be interesting to watch whether such chemotherapy-induced changes may cause discrepancies in the predictive power of potential molecular biomarkers of benefit from immunotherapy such as the TCGA Clusters between the pretreated and treatment-naïve settings. Indeed, in the smaller phase II study of first-line atezolizumab in cisplatin-unfit patients (11), the higher efficacy of the anti-PD-L1 in TCGA cluster II tumors is much less apparent than in the second-line setting (9), suggesting that chemotherapy-induced changes in this specific subtype may partake of immunotherapy efficacy.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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