Commentary

Predicting response to neoadjuvant chemotherapy in bladder cancer: controversies remain with genomic DNA sequencing

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Submitted Jan 18, 2016. Accepted for publication Jan 18, 2016.

doi: 10.21037/tau.2016.02.01

View this article at: http://dx.doi.org/10.21037/tau.2016.02.01

Neoadjuvant cisplatin-based chemotherapy (NAC) in muscle-invasive bladder cancer is an accepted standard of care (1,2). NAC improves patient outcomes quantified by a 5–8% higher 5-year overall survival (OS) and an increase of pathological downstaging of 10–15% (3-5). However, a considerable number of patients do not response to NAC. They are over treated and suffer from unnecessary adverse effects. This led biomarker researchers focus on the prediction of response to NAC (6-11), including the recently published study carried out by Plimack *et al*., which performed genomic DNA sequencing of pretreatment tumor tissue (12).

They used two independent cohorts, enrolled of clinical trials, for discovery (n=34) and validation (n=24). The NAC regimens were accelerated methotrexate, vinblastine, doxorubicin, and cisplatin (AMVAC) (13) in the discovery cohort and dose-dense gemcitabine and cisplatin (DDGC) (14) in the validation cohort. Of pretreatment tumor samples, DNA alterations in 278 cancer-related genes were determined. They discovered a decision tree based on alterations of three genes (ATM, RB1, and FANCC), which was able to predict pathologic downstaging (≤ pT1pN0cM0), complete response (pT0pN0cM0) as well as progression free survival (PFS) and OS. None of the nonresponders in the discovery cohort had an alteration in one of these genes. In the validation cohort, this decision tree was partially significant. About 64% patients with pathological downstaging and only 15% nonresponders had at least one alteration in one of these genes (P=0.033). Although, the Kaplan-Meier curves for RFS and OS looks discriminative, only the log-rank test for OS was almost significant (P=0.055). However, this cohort is smaller, the follow up shorter, the included patients older and with a higher ECOG, which questions RFS and OS as appropriate endpoints.

Intuitively, it seems evident that these DNA repair-associated genes (ATM, RB1, and FANCC) are related to the response to NAC. But DNA alterations do not necessarily reflect functional and structural changes of a given protein. To investigate the potential biological consequence of a given alteration, they used computed prediction models. Indeed the vast majority of alterations were predicted to be deleterious. However, only structural analysis of the proteins and the subsequent loss of their biological function may allow to prove the consequences of these genomic DNA alterations.

Recently two other groups investigated genomic DNA alterations of pretreatment tumor tissue and related their findings with likelihood of response to NAC (7,11). Van Allen *et al*. discovered that somatic mutations in ERCC2, a gene related to DNA-repair, were associated with favorable response (11). Interestingly, they proved their findings *in vitro* and showed that ERCC2-deficient cell lines failed to rescue cisplatin sensitivity. Groenendijk *et al*. found that only complete responders but none of the nonresponders showed missense mutations in ERBB2 (7). The trend for more missense mutations in ERCC2 in complete responders was not significant.

Interestingly, all groups identified different genomic DNA alterations. Several reasons could explain this inconsistency. The rather small cohorts (range, 24–71), differences in cohort enrolment and NAC regimens might influence the discovery. The clinical stages of these cohorts are comparable but there are differences in practice patterns. While NAC is considered in all patients with muscle-invasive bladder cancer in North America, this is less common in Europe where NAC is predominantly suggested for higher staged patients. Therefore, the rate of surgical downstaging may be different. Since surgically

down-staged tumors are indistinguishable from tumors that respond to chemotherapy, there is a higher risk in a North American patient cohort that biologically resistant tumors are erroneously classified as chemoresponsive. In addition, all studies used different criteria to define the response to NAC. Van Allen *et al.* did not consider lymph node positive cases as non-responders and Groenendijk *et al.* excluded patients with invasive organ confined residual tumors. Plimack *et al.* not only compared nonresponders with complete responders but also with those that had pathologic downstaging and they included survival as secondary endpoint. Finally, all studies used different sequencing methods. Van Allen *et al.* performed whole exome sequencing, whereas the two others (7,12) used targeted sequencing of cancer-related genes. Importantly, the panel used by the Plimack *et al.*, did not include ERCC2, what prevented a potential validation.

Two studies reported a common finding (11,12). Responders had a significantly higher rate of somatic mutations when compared with non-responders. In general, bladder cancer as well as other cancers induced by carcinogens such as tobacco smoke shows a higher rate of somatic mutations (15,16). A somehow ironic consequence may be that smokers respond better to NAC than nonsmokers. Only Van Allen *et al.* provided smoking status but this data did not show a trend that supports this hypothesis (11). However, this could be an interesting question for future studies investigating genomic DNA alterations in relation with response to NAC.

A definitive validation of these findings is still needed. Ideally, future cohorts should be larger, treated with a specific chemotherapy regimen, combined with a chemonaive cohort to define the biomarker as predictive rather than prognostic and include all genes of interest. Another open question is the appropriate study endpoint. The nature is rarely black or white and why should this be the case in response to NAC? I would suggest a three-graded system for example as follows: Complete, partial and non-responders. Patients without remaining tumor are obviously complete responders. Patients with urothelial in-situ carcinoma and non-invasive papillary tumors should also be categorized as complete responders. These tumors are rarely lethal, are not treated with cisplatin and have similar outcomes when compared with patients without residual tumors (17). Patients with extravesical extension of the remaining primary tumor and lymph node metastasis should be categorized as non-responders. But how would we categorize patients with invasive organ confined residual tumors? Several studies showed similar outcomes of patients with organ confined residual tumors invading into the submucosa and muscle, respectively (4,17,18). More importantly, patients with muscle-invasive organ confined disease had a significant better outcome than those with extravesical extension of residual tumors. Therefore, I would categorized those patients with invasive but organ confined residual tumors as partial responders. An advantage of the suggested three categories would be that surgical downstaging of nonresponders is very unlikely. We might also include other parameters, for example histological signs and regression in surgical specimens after NAC. Recently, we described these histological signs and suggested a tumor regression grade that categorizes response to NAC (19). But these findings need to be validated in larger datasets before being taken into account for newly defined categories. In addition, we might also be able to identify biomarkers assessed in residual tumors that define response to NAC. Eventually, a combination of pathological staging, histological assessment and biomarkers might be used to define new categories. Of course, these suggested categories are pure speculation. But the fact is that all three studies (7,11,12) used different patient categories with regard to response to NAC. This indicates that its definition suggested in the literature is not generally accepted. Therefore, a valid definition of response to NAC will be essential for future biomarker studies.

Acknowledgements

None.

Footnote

Provenance: This is a Guest Commentary commissioned by the Editorial Board Member Xiongbing Zu (Department of Urology, Xiangya Hospital, Central South University, Changsha, China).
Conflicts of Interest: The author has no conflicts of interest to declare.

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Cite this article as: Seiler R. Predicting response to neoadjuvant chemotherapy in bladder cancer: controversies remain with genomic DNA sequencing. Transl Androl Urol 2016;5(2):271-273. doi: 10.21037/tau.2016.02.01

