Editorial

Biomarkers for platinum sensitivity in bladder cancer: are we there yet?

Nirmish Singla, Rashed A. Ghandour, Ganesh V. Raj

Department of Urology, University of Texas Southwestern Medical Center, Dallas, TX, USA

Correspondence to: Ganesh V. Raj, MD, PhD. Department of Urology, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX, USA. Email: ganesh.raj@utsouthwestern.edu.

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The current standard of care for treating patients with newly diagnosed muscle-invasive bladder cancer (MIBC) is the administration of neoadjuvant cisplatin-based chemotherapy (NAC) followed by radical cystectomy (RC) in surgical candidates. This recommendation is based on level 1 evidence demonstrating improved overall survival for NAC followed by RC compared to RC alone (1,2). The survival benefit from the use of NAC is largely attributable to pathologic downstaging of the primary tumor (3) and the potential eradication of micrometastatic disease.

Although this paradigm has been endorsed by multiple clinical guidelines (2,4), it is clear that this "one-size-fits-all" approach of offering NAC to all eligible MIBC patients with adequate renal function is not appropriate for every patient. The majority of MIBC patients do not benefit from NAC. Further neoadjuvant therapies may unnecessarily delay surgery and subject patients to the significant side effects of chemotherapy (5-7). The ability to predict which MIBC patients will and will not respond to NAC would undoubtedly redefine our current treatment algorithms by appropriately stratifying patients to receive either NAC followed by RC, upfront RC, or perhaps even alternative frontline systemic therapies such as immunotherapy.

The concept of dichotomizing MIBC patients into "primary" (i.e., those presenting with *de novo* MIBC) and "secondary" [i.e., those initially diagnosed with non-muscle-invasive disease (NMIBC) who subsequently progressed to MIBC] cohorts has been explored in several prior studies. In a recent systematic review and meta-analysis, Ge *et al.* evaluated the oncologic outcomes of patients with primary and secondary MIBC across 14 studies since 2002, including two prospective studies (8). While their meta-analysis demonstrated slightly inferior survival outcomes in secondary MIBC patients than in primary MIBC patients overall, their results ought to be interpreted cautiously given the heterogeneity among the included studies.

In their recent article, Pietzak *et al.* sought to further characterize chemosensitivity and chemo-resistance patterns in MIBC patients by correlating clinical response to chemotherapy with genomic differences between primary and secondary MIBC (9). Their overall hypothesis was that secondary MIBC would have an increased mutation burden, due to prior exposure to intravesical therapies. Their clinical findings were quite compelling, in that patients with primary MIBC demonstrated significantly greater pathologic response rates (≤ pT1N0)—nearly twice that of secondary MIBC (45% *vs.* 26%, P=0.02). Even more striking was the observation that no patients in the secondary MIBC group achieved complete pathologic response (0% pT0 rate), compared to 15% in the primary MIBC group. Multivariable analyses supported their findings, suggesting that treatment-naïve or primary MIBC patients may exhibit a better response to NAC compared to secondary MIBC. Not surprisingly, this translated to significantly superior recurrence-free (RFS) and overall survival (OS). Importantly, their data indicates

that administration of NAC to patients with secondary MIBC actually worsened cancer-specific survival (CSS), OS, and RFS compared to those secondary MIBC patients undergoing upfront RC. The authors suggest that offering NAC to secondary MIBC patients may result in suboptimal outcomes, by delaying potentially curative surgery. In contradistinction, consistent with results expected from the original SWOG-8710 trial (1), NAC effectively improved oncologic outcomes in patients with primary MIBC. Taken together, these findings strongly support consideration of the primary versus secondary status of MIBC in the decision to use NAC.

There are important caveats to consider when interpreting these clinical data. As the majority of the secondary MIBC cases were referred, the initial diagnosis and management of the corresponding NMIBC "phase" were performed elsewhere. Hence, it is not known whether these patients were truly non-muscle-invasive at diagnosis or if a subset were actually muscle-invasive at diagnosis but understaged and hence inappropriately managed. In addition, the time from diagnosis of muscle-invasive cancer to initiation of treatment must be factored, since treatment delay has been shown to adversely affect treatment outcomes (10). The likely heterogeneous nature of intravesical therapies received in the NMIBC phase also limits the ability to interpret treatment-induced tumor clonal selective pressures. Of note, the well-annotated BCG clinical trials performed at Memorial Sloan Kettering Cancer Center in the 1980s may enable the investigators to more clearly address the differences in outcomes between primary and secondary MIBC (11). Finally, as clinical analysis was performed retrospectively, further prospective validation is warranted in secondary MIBC patients.

To explore their clinical observations further, the authors also evaluated genomic differences between primary and secondary MIBC. Recently, efforts from other groups have been made to elucidate genomic drivers of chemosensitivity in MIBC using next-generation sequencing. Alterations in the DNA damage repair (DDR) genes *ERCC2* (12), *ATM*, *RB1*, and *FANCC* (13) and mutations in the receptor tyrosine kinase gene *ERBB2* (14) have been proposed to confer increased sensitivity and greater pathologic response to cisplatin-based chemotherapy. Using similar sequencing efforts, the authors determined that deleterious somatic missense mutations in *ERCC2* were significantly more common in patients with primary MIBC compared to those with secondary MIBC in both their discovery (11% *vs.* 1.8%, P=0.04) and validation (15.7% *vs.* 0%, P=0.03) cohorts. These data are consistent with increased chemosensitivity seen in primary MIBC. It is conceivable that the enrichment of *ERCC2* alterations in their primary MIBC cohort may be largely attributable to the selective eradication of *ERCC2*-mutant tumor clones in the secondary MIBC cohort by intravesical BCG therapies received in the NMIBC phase, given that *ERCC2* mutations may confer greater sensitivity to intravesical BCG as well (15).

Despite significant findings with *ERCC2*, however, alterations in other DDR genes including *ATM*, *RB1*, and *FANCC* and in *ERBB2* did not differ significantly between groups in their study. On targeted sequencing, primary MIBC tumors appeared to have a higher mutational burden than secondary MIBC tumors, but this was not confirmed by more comprehensive whole-exome sequencing. Earlier studies have also suggested that response to cisplatin-based chemotherapy may be driven, at least in part, by basal versus luminal molecular subtyping (16,17). However, in Pietzak *et al.*'s cohort, differential enrichment of molecular subtypes did not differ between primary and secondary MIBC (9).

Undoubtedly, the results for *ERCC2* are both exciting and encouraging. However, they are insufficient to explain entirely the chemosensitivity differences between primary and secondary MIBC and likely represent just the tip of the iceberg. *ERCC2* missense mutations account for only 12% of MIBC tumors in The Cancer Genome Atlas (12,18), and *ERCC2* represents only one of many genes in the DDR class. Poly(adenosine diphosphate [ADP]-ribose) polymerase (PARP) deserves comment, given its involvement in various mechanisms of DNA repair (19). Inhibitors of this enzyme have been used therapeutically in other malignancies, such as ovarian, breast, and prostate cancer (20). Consistent mechanistically, aberrations in DDR genes have also been proposed as potential markers for sensitivity to PARP inhibitors (21). For example, in the setting of metastatic castrate-resistant prostate cancer (mCRPC), investigators of the recent TOPARP-A trial reported that patients harboring DDR gene alterations exhibited a strikingly favorable response to olaparib (20). Considering the mechanism of platinum-based chemotherapy, we postulate that the DDR defects reported in their trial—which included *BRCA2*, *ATM*, *BRCA1*, *PALB2*, *CHEK2*, *FANCA*, and *HDAC2*—may be associated with platinum sensitivity as well. While Pietzak *et al.* interrogated a subset of these DDR genes in their study (9), a more comprehensive unbiased evaluation of other DDR genes may further improve our ability to predict response to chemotherapy.

In addition, continued improvement in imaging

protocols involving multiparametric MRI (mpMRI) has helped increase the accuracy of local staging in bladder cancer (22-24). By better defining tumor extent and depth into the detrusor muscle, even after transurethral resection (25), mpMRI may help reduce issues related to understaging true primary MIBC as NMIBC that is then later reclassified as "secondary" MIBC after inappropriate treatment. Indeed, the growing integration of mpMRI features with genomics may help identify promising radiomic markers to better assess stage and treatment response in patients with MIBC (26,27).

Although a purely biomarker-driven approach to offering NAC in the MIBC setting may not be quite ready for primetime yet, clinicians should, at the least, take pause before routinely offering NAC to patients with secondary MIBC—particularly those who have been heavily pre-treated in the NMIBC phase—based on the results of the study by Pietzak *et al.* (9). Perhaps a genomic exploration in these patients may provide further information to help guide clinical decision-making, such as the utility of upfront RC or the use of investigational targeted therapies. Prospective validation of their findings with more direct integration of genomic or radiomic differences with cisplatin response, as in the ongoing SWOG-1314, COXEN trial (NCT02177695), is eagerly awaited. It is our hope that these data will continue to improve the outcomes for patients with primary or secondary MIBC.

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Footnote

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

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