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Re: Genomic Differences Between "Primary" and "Secondary" Muscle-invasive Bladder Cancer as a Basis for Disparate Outcomes to Cisplatin-based Neoadjuvant Chemotherapy

Pietzak EJ, Zabor EC, Bagrodia A, et al

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Experts' summary:

The authors investigated whether patients with non-muscle-invasive bladder cancer (NMIBC) who experience progression to muscle-invasive bladder cancer ("secondary" MIBC) differ in clinical outcome and chemosensitivity compared to patients presenting with "primary" MIBC [1]. A retrospective analysis of clinical data from an MIBC patient cohort was performed (clinical stage T2–4aN0M0 disease, ≥3 cycles of neoadjuvant chemotherapy [NAC]). Pathologic response at radical cystectomy (RC) was defined as ≤pT1N0. Pathologic response was lower in patients with secondary MIBC on both univariate (26% vs 45%; $p = 0.02$) and multivariable analyses (odds ratio 0.4, 95% confidence interval 0.18–0.84; $p = 0.02$). Moreover, secondary MIBC was associated with worse recurrence-free survival ($p < 0.007$) and overall survival ($p = 0.048$). Next, they showed that of the somatic genomic alterations in genes implicated in platinum-based chemotherapy response in MIBC (*ERCC2*, *ATM*, *FANCC*, and *RB1*), only *ERCC2* mutations account for this difference in clinical outcome and chemosensitivity between primary and secondary MIBC [2,3]. *ERCC2* missense mutations were enriched in primary versus secondary MIBC (11% vs 1.8%; $p = 0.044$) and findings validated in an independent prospective cohort confirmed enriched *ERCC2* mutations in primary versus secondary MIBC tumors (17.1% vs 0%; $p = 0.033$).

The authors conclude that upfront RC or enrollment in clinical trials should be considered for patients with secondary MIBC because of the marginal clinical benefit of NAC.

Experts' comments:

This study highlights the current overall weakness of biomarkers in predicting response to NAC. As a surrogate, the authors suggest using secondary MIBC to identify patients who might benefit from upfront RC or could be considered for clinical trials. Prior studies have already demonstrated worse clinical outcomes for secondary compared to primary MIBC [4]. Up to now, this worse outcome was explained by secondary MIBC patients having received multiple ineffective bacillus Calmette-Guérin (BCG) instillations, leading to a delay in RC. This is the first study to demonstrate that secondary MIBC patients have a lower response to NAC than primary MIBC patients, and that this could be caused by a difference in genomic make-up of the tumors. Importantly, the authors showed few *ERCC2* mutations in secondary MIBC. Despite the retrospective nature of this study, these interesting findings raise the question of whether resistance to NAC in secondary MIBC is an intrinsic tumor feature or is acquired during treatment with BCG (treatment selection of clones resistant to subsequent NAC). Since our molecular insights are still quite limited, to answer this question, additional studies profiling NMIBC patients at a high risk of developing progression are urgently needed to elucidate the genomic landscape of these tumors [5].

Conflicts of interest: The authors have nothing to disclose.

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