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Platinum Priority – Editorial

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ERCC2 Mutation: The Marker for Chemosensitivity in Primary and Secondary Muscle-invasive Bladder Cancers

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Cisplatin-based combination chemotherapy followed by radical cystectomy (RC) is the standard frontline treatment option for bladder cancer, yielding pathologic responses in approximately half of patients. The recent development of high-throughput technologies may allow us to predict responses to chemotherapy in bladder cancer. With respect to the molecular subtypes defined on the basis of gene expression profiling data, the basal subtype has been associated with the greatest survival benefit, while the p53-like/infiltrated subtype was associated with resistance [1,2]. Using MSK-IMPACT (Memorial Sloan-Kettering Cancer Center) and other panel DNA exome sequencing platforms, the predictive value of alterations in genes involved in DNA repair has been demonstrated. In particular, defects in *ERCC2* were correlated with response in patients with muscle-invasive bladder cancer (MIBC) [3]. Another study found that alterations in one or more of three genes associated with DNA repair—*ATM*, *RB1*, and *FANCC*—could predict pathologic response and survival outcomes [4]. These biomarkers were validated in independent data sets [5] and are now being evaluated prospectively in ongoing clinical trials.

Secondary MIBCs are cancers that progress from non–MIBC (NMIBC); on a stage-for-stage basis, they are associated with poorer clinical outcomes compared to primary MIBCs [6,7]. In this issue of *European Urology*, Pietzak and colleagues [8] characterize the clinical and genomic differences between primary and secondary MIBCs from patients treated with neoadjuvant chemotherapy (NAC) and RC. They observed lower pathologic response rates and survival for secondary compared to primary MIBCs, consistent with previous observations. Furthermore, survival outcomes were no better among patients with secondary MIBCs who were treated with NAC plus RC than those observed for patients treated with surgery alone, whereas NAC improved survival outcomes among patients with primary MIBCs, suggesting that secondary MIBCs as a class might be resistant to chemotherapy. In the analysis, delay of RC because of NAC treatment for secondary MIBCs significantly contributed to the worse survival outcomes. In two independent genomic cohorts, *ERCC2* mutations were significantly enriched in primary as compared to secondary MIBCs, and the authors concluded that the lack of *ERCC2* mutations in secondary MIBCs contributed to resistance. Alterations in the other DNA repair genes previously validated (*ATM*, *RB1*, and *FANCC*) were also evaluated, but mutation frequencies between the primary and secondary MIBCs were not significantly different. Furthermore, the authors did not observe any association between molecular subtype and outcomes using two different classifiers (the University of North Carolina [UNC] BASE47 two-subtype classifier and The Cancer Genome Atlas [TCGA] five-subtype classifier) [9,10].

Evidence for the importance of DNA damage and repair mutations in dictating response to cisplatin-based combination chemotherapy in patients with bladder cancer continues to accumulate, and definitive confirmation of their importance as biomarkers could be available within a year as a consequence of ongoing studies using tumors from the Southwest Oncology Group S1314 clinical trial. However, it would be premature to withhold chemotherapy from patients with primary or secondary MIBCs whose tumors do not contain mutations or deletions in these genes. *ERCC2* is mutated in 10–16% of MIBCs, whereas modern NAC regimens produce clinical responses in more than half of patients, so additional mechanisms of sensitivity must exist. Importantly, the experiments in the current study were not performed

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with matched primary and secondary MIBCs, and the cohort sizes are relatively small. Therefore, the results should be validated with matched tumors in future research. Finally, additional studies should be performed to explore tumor molecular subtypes in primary and secondary MIBCs. Although progress is being made, there is still no firm consensus in the bladder cancer research community with regard to which subtyping strategy is most biologically and/or clinically relevant. Unlike others [1,2,11], the relationship between molecular subtype and treatment response in tumors classified using the two methods described here (UNC and TCGA subtypes) has not been established. Therefore, it may an overstatement to suggest that there is no association between molecular subtype and clinical outcomes in secondary MIBCs. It is also possible that integration of molecular subtypes and DNA damage and repair alterations into a combined classifier could improve clinical decision-making for patients with either primary or secondary MIBCs.

The study by Pietzak et al. [8] sheds important new light on the clinical and genomic differences between primary and secondary MIBCs. After the completion of ongoing validation studies, we hope that mutations in *ERCC2* and other DNA damage and repair genes will become clinically available biomarkers to select patients for treatment with neoadjuvant chemotherapy.

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