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CCR Translations

Clinical Cancer Research

DNA Damage Response Gene Alterations in Urothelial Cancer: Ready for Practice?

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Cisplatin-based neoadjuvant chemotherapy prior to radical cystectomy is standard in fit patients. Inactivating mutations of the nucleotide excision repair gene *ERCC2* can predict response to cisplatin-based chemotherapy. Evaluation of the functional impact of ERCC2 mutations can provide mechanistic frameworks supporting the potential predictive role of ERCC2 loss of function.

See related article by Li et al., p. 977

In this issue of *Clinical Cancer Research*, Li and colleagues sought to evaluate the functional impact of missense mutations in the nucleotide excision repair (NER) gene *ERCC2* and the association with response to cisplatin-based chemotherapy (1). Alterations in DNA damage response (DDR) genes have potential role in the management of urothelial cancer, a disease that has suffered from the complete absence of molecular biomarkers with proven clinical utility. Even if not instantly practice changing, the findings are highly relevant in the field of urothelial cancer research.

A relevant biomarker should have "preanalytic and analytic validity," meaning it should measure accurately the relevant analyte or parameter. Moreover, it needs to demonstrate "clinical validity" or "biological relevance," related to its ability to predict distinct outcomes in biomarker-defined patient populations. However, biomarkers cannot be incorporated routinely in clinical practice unless they exhibit "clinical utility," related to evidence of improved outcomes when used in decision making. The latter is a frequent pitfall in biomarker development with numerous putative biomarkers failing to meet this high standard. The "lifetime" of a developing biomarker frequently starts with "*in silico*" and database evaluation, *in vitro* mechanistic and functional assays, *in vitro* and *in vivo* assessment of its impact on disease models, and retrospective evaluation in human disease datasets, followed by prospective assessment in clinical studies. The last step is critical to demonstrate "clinical utility" as the ultimate test before incorporation into practice.

At the era of molecular medicine and deep next-generation sequencing there is a plethora of newly identified genomic alterations that may inform the discovery and validation of putative biomarkers. The increasing variety of genomic platforms with various gene panels and bioinformatics assays generates large datasets that can be interrogated for "actionability."

Li and colleagues elegantly developed a microscope-based assay to directly measure the NER capacity of *ERCC2* mutations and reported that mutations in the helicase domain functionally impair NER. They also developed a preclinical *ERCC2*-deficient bladder cancer model to demonstrate that *ERCC2* loss of function was sufficient to mediate cisplatin sensitivity. These data provided further mechanistic validation of prior findings by Liu and colleagues nominating *ERCC2* alterations as a biomarker of response to neoadjuvant cisplatin-based chemotherapy in independent bladder urothelial cancer cohorts (2). In their validation study, 8 of 20 responders (40%) and 2 of 28 nonresponders (7%) had nonsynonymous ERCC2 alterations ($P = 0.01$); moreover, there was significantly longer overall survival in patients with *ERCC2* alterations in both the validation ($P = 0.03$) and discovery cohort ($P = 0.049$). However, those alterations were not shown to be present only in responders to cisplatin-based chemotherapy. Even in nonresponders, *ERCC2* mutations can be in the same (peri-) helicase regions, while they were found only in 40% of responders, implying that other possible biomarkers may affect treatment response. In addition, Plimack and colleagues had reported that alterations in 3 other genes (*ATM*, *Rb1*, and *FANCC*) also predicted response to cisplatin-based neoadjuvant chemotherapy and overall survival (3). On the basis of these data, there can be complementary roles of several DDR gene alterations that may impact the ability of cancer cells to repair cisplatin-induced DNA damage. Detailed cataloging, characterization, and evaluation of DDR gene alterations can lead to the development of more comprehensive integrated panels that may inform clinical decision making after prospective validation. In addition, Teo and colleagues reported that somatic DDR gene alterations were associated with better outcomes in platinum-treated patients with advanced urothelial cancer, suggesting that the potential implications of DDR gene alterations are not specific in the neoadjuvant treatment setting (4).

On the basis of the above observations, the study by Li and colleagues further supported *ERCC2* alterations as a biomarker predictive of response to cisplatin-based chemotherapy in urothelial cancer and underlined the potential to combine both genomic and functional methods to guide precision oncology. Evaluation of the functional impact of genomic alterations is very important; however, it is faced with pragmatic challenges regarding the applications in the "fast-pace" clinical practice, for example, how practical is to assess the functional role of a variant of unknown significance for clinical trial eligibility or other treatment decisions? Overall and based on the very promising data, the paradigm of DDR gene alterations as "actionable and clinically useful biomarker" certainly merits prospective evaluation in clinical trials. This is further supported by data suggesting that DDR gene alterations were also strongly associated with response to

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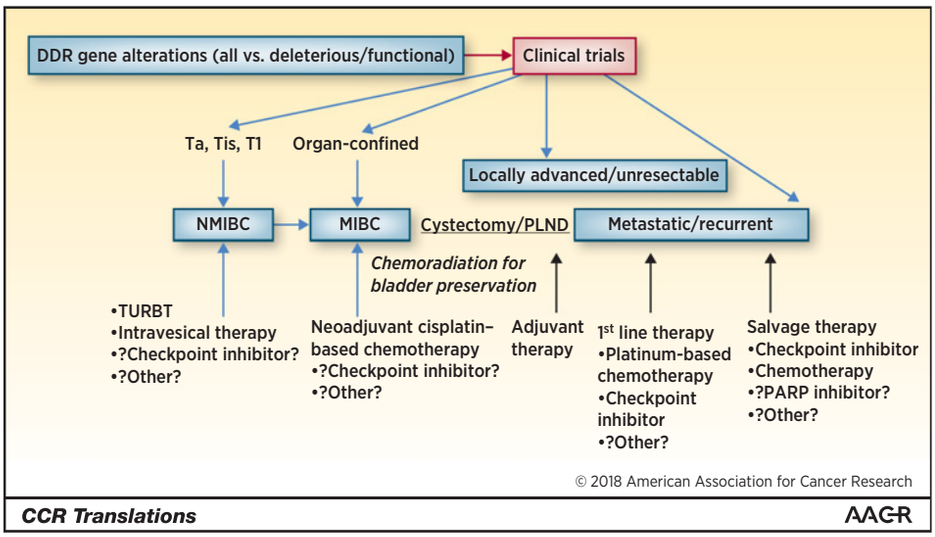

Figure 1.
Schematic presentation of the spectrum of treatment settings in urothelial cancer and potential clinical applications of DDR gene alterations as biomarkers. MIBC, muscle-invasive bladder cancer; NMIBC, non–muscle invasive bladder cancer; PLND, pelvic lymph node dissection.

immune-checkpoint inhibitors in urothelial cancer (5). The question also extends into whether such alterations may help predict response to PARP inhibitors that are being tested in this disease.

There are several relevant clinical trials evaluating the role of DDR gene alterations in urothelial cancer. In the neoadjuvant setting, an open label phase II trial aims to evaluate a risk-adapted approach in localized bladder urothelial cancer (RETAIN BLADDER; NCT02710734). Each baseline transurethral resection of bladder tumor (TURBT) biospecimen will be sequenced while proceeding with neoadjuvant cisplatin-based chemotherapy. On the basis of the genomic profile and the postchemotherapy TURBT findings, patients will be treated with either active surveillance or intravesical therapy, chemoradiation or surgery, with 2-year metastasis-free survival being the primary endpoint. A cooperative group (A031701) phase II trial of dose-dense gemcitabine/cisplatin in localized bladder urothelial cancer is also evaluating potential bladder preservation in patients with tumors harboring deleterious DDR gene alterations (NCT03609216); primary endpoint is the 3-year event-free survival within the bladder-sparing group. Another trial is testing gemcitabine/cisplatin chemotherapy combined with the anti-PD1 agent nivolumab in localized bladder urothelial cancer (NCT03558087). The primary endpoints are to determine the clinical complete response rate with the used regimen as well as the ability of this metric to predict further clinical benefit, defined as pathologic complete response in patients undergoing cystectomy and 2-year metastasis-free survival in those pursuing active surveillance. Those trials aim to prospective validate the association between DDR gene alterations and clinical benefit, and have the potential to impact clinical practice. However, in the time being, patients who undergo neoadjuvant cisplatin-based chemotherapy should not forgo local definitive therapy outside the clinical trial context.

Notably, several clinical trials have been evaluating the association between DDR gene alterations and response to immune-checkpoint inhibitors (either as single agent or part of combination regimens) as exploratory endpoints. In the advanced disease setting, DDR gene alterations are used as trial eligibility criteria, for example, in an "umbrella" trial (BISCAY; NCT02546661) that includes multiple treatment modules, including one with anti-PDL1 agent combined with PARP inhibitor. Different phase II trials are evaluating the efficacy of PARP inhibitor monotherapy in advanced urothelial cancer and can shed further light into the relationship between DDR gene alterations and response to PARP inhibitors (NCT03448718; NCT03397394). Last, but not least, the NCI-MATCH trial is an example of "basket" trials that use genomic-based biomarkers for eligibility and module allocation; this research paradigm is expected to investigate more broadly the clinical "actionability" of DDR gene alterations across tumor types.

To conclude, the findings by Li and colleagues provide a solid foundation about how mechanistic and functional approaches can complement clinical observations and previously validated findings. Ongoing clinical trials that incorporate relevant biomarkers provide an ideal setting for prospective evaluation of DDR gene alterations and hold the promise to meaningfully change the treatment landscape in urothelial cancer (Fig. 1) by applying principles of systems biology and precision oncology. Accrual in clinical trials and alignment of correlative studies are critical for urothelial cancer research progress.

Disclosure of Potential Conflicts of Interest

P. Grivas reports receiving other commercial research support from Clovis Oncology, Pfizer, AstraZeneca, Merck & Co., Genentech, Mirati, Bayer, and Oncogenex, has received speakers bureau honoraria from Genentech and Bristol-Myers Squibb, and has been a consultant/advisory board member for Merck & Co., Dendreon, Bristol-Myers Squibb, Genentech, AstraZeneca, Clovis Oncology, EMD Serono, Pfizer, Biocept, Foundation Medicine, Seattle Genetics, Driver Inc., QED Therapeutics, Exelixis, Bayer, and Heron Therapeutics. No other potential conflicts of interest were disclosed.

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