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Seminars article

Novel biomarkers in bladder cancer

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Abstract

A sea change has occurred in the treatment options available for metastatic urothelial bladder cancer with the recent Food and Drug Administration approval of 5 immune checkpoint blockade agents for patients who have progressed on platinum-based chemotherapy or are not candidates for cisplatin. Additionally, comprehensive characterization of the landscape of genomic alterations in this disease through The Cancer Genome Atlas and other efforts has detected numerous potential targets for small molecule inhibitors. Detailed analysis of the urothelial carcinoma transcriptome has allowed for molecular subtyping of the disease and the ramifications of these subtypes upon treatment response is an active area of investigation. Coupled with these advances is a critical unmet need to define predictive biomarkers of response to therapy. Here, we highlight select research relevant to the validation and continued discovery of novel biomarkers to advance precision oncology in bladder cancer.

Keywords: Biomarkers; Bladder cancer; Urothelial carcinoma

Introduction

Assessment of tumor tissue for genomic biomarkers predictive of sensitivity or resistance to specific therapies is part of standard of care management for advanced or metastatic cancers in a limited number of solid tumor malignancies. Examples of single gene alterations which guide treatment with Food and Drug Administration (FDA)-approved targeted therapies include BRAF V600 activating mutations in metastatic melanoma, as well as EGFR, ALK, and ROS1 alterations in metastatic non–small cell lung cancer. In metastatic colorectal cancer, the presence of mutant RAS guides against the inclusion of anti-EGFR antibodies such as cetuximab. Predictive biomarkers are also employed in treatment selection for immunotherapy in specific settings. Assessment of PD-L1 expression to establish eligibility for first-line, single agent pembrolizumab is a standard for non–small cell lung cancer. Pembrolizumab is also FDA-approved in advanced or metastatic solid tumors that are microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) [1,2]. This represents the first tissue agnostic FDA approval based solely upon a specific genetic feature. Although an increased understanding of the genomic and transcriptomic landscape of urothelial bladder cancer has resulted from recent large-scale analyses [3,4], no standard-of-care biomarkers are currently employed to guide management in this disease. Urinary bladder cancer is responsible for nearly 17,000 deaths annually in the United States [5], and while several immune checkpoint agents have become approved recently in the metastatic setting, current treatment options for advanced or metastatic disease exhibit limited response rates and can result in significant morbidity [6–8]. Pembrolizumab benefit was independent of PD-L1 status in the phase III trial of this therapy in the second-line setting [7]. Investigation of novel biomarkers to biologically stratify bladder cancer patients for precision cancer care represents a critical priority.

Genomic biomarkers

Stratification by p53 status for adjuvant chemotherapy

The first trial in bladder cancer to stratify management based on a molecular alteration assessed whether p53 status

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may be predictive of benefit for adjuvant chemotherapy following cystectomy. This phase III trial assessed p53 expression in 499 patients with stage pT1/T2N0M0 urothelial cancer of the bladder following radical cystectomy and bilateral pelvic lymphadenectomy [9]. A total of 272 patients (55%) were considered altered for p53, as defined by ≥10% nuclear immunoreactivity reflecting accumulation mediated by abnormally prolonged protein half-life. These patients were then randomized to adjuvant chemotherapy with 3 cycles of combination methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) vs. observation. Notably, only 114 patients (42%) from this group consented to randomization, and only 46 of the 58 patients assigned to adjuvant MVAC received therapy. No difference in recurrence was observed between the randomized arms (HR 0.78; CI: 0.29–2.08; $P = 0.62$). Furthermore, there was no difference in the overall 5-year probability of recurrence between p53-positive and p53-negative patients. This trial was limited by the low rate of consent for randomization as well as limited compliance with adjuvant chemotherapy when assigned.

Correlation of somatic ERCC2 mutations with cisplatin sensitivity

Neoadjuvant cisplatin-based chemotherapy followed by radical cystectomy is a standard of care treatment option for muscle-invasive bladder cancer and long-term survival has been strongly correlated with the extent of down-staging to non–muscle-invasive disease as assessed at radical cystectomy [10,11]. In an extreme responder approach performed by Van Allen et al. [12], whole exome sequencing was performed using DNA from pretreatment transurethral resection specimens and matched germline DNA from 50 patients who received neoadjuvant cisplatin-based chemotherapy to assess genomic correlates of response. This analysis identified that somatic mutations in ERCC2, a gene involved in nucleotide excision repair, were enriched in the 25 patients who had no residual invasive disease compared to the 25 non-responders with pT2 or higher stage disease at cystectomy. Notably, all nonsynonymous ERCC2 mutations occurred in the responder cohort (9 of 25 vs. 0 of 25 in non-responders, $P < 0.001$; Fisher exact test), and no other genes demonstrated significant enrichment in this group. Functional validation of a subset of these ERCC2 mutants suggested that they confer sensitivity to platinum. Expression of mutant or wild-type ERCC2 in an nucleotide excision repair impaired cell line that exhibits sensitivity to platinum-induced damage resulted in reversal of this platinum sensitivity phenotype only with wild-type ERCC2 and none of the mutants. A subsequent analysis employing targeted exon sequencing of 287 genes on tumor tissue from 58 patients who received neoadjuvant cisplatin-based chemotherapy found that a mutation in any 1 of 3 genes (RB1, FANCC, or ATM) was associated with improved response to chemotherapy in both a discovery and validation cohort [13]. In a third analysis, an association of somatic ERCC2 alterations with response, defined as pT0/pTis/pTa disease at cystectomy, was explored in a cohort of 48 patients with MIBC who received neoadjuvant chemotherapy. Forty percent (8/20) of responders had nonsynonymous ERCC2 mutations compared to 7% (2/28) of non-responders [14]. Furthermore, a statistically significant difference in overall survival favoring patients with ERCC2 mutations was observed in this validation cohort, as well the previously described Van Allen cohort [12]. In a separate analysis, tumor tissue from 100 advanced or metastatic urothelial carcinoma patients treated with first-line platinum-based chemotherapy underwent targeted next-generation sequencing (NGS) using the MSK-IMPACT assay [15,16]. The presence of mutations in ERCC2, which occurred in 5% of this cohort, was not significantly associated with outcome. However, the presence of an alteration in one or more of the 34 DNA damage response and repair (DDR) genes included in the NGS panel was associated with both improved progression-free and overall survival [17]. Notably, 44% of the patients in this cohort received carboplatin-based therapy rather than cisplatin-based therapy. Overall, these retrospective data suggest that mutations in ERCC2 and other DDR genes may represent genomic biomarkers to identify patients with the greatest likelihood to benefit long-term from cisplatin-based chemotherapy. These data comprise the rationale for a planned prospective cooperative group trial which will assess a bladder-sparing approach in patients with muscle-invasive bladder cancer who achieve clinical down-staging to non-invasive disease following cisplatin-based chemotherapy in patients with deleterious alterations within a pre-specified DDR gene panel.

Mutation load and response to PD-L1 blockade

Several checkpoint inhibitors are approved for the treatment of metastatic urothelial carcinoma, including atezolizumab, a humanized antibody targeting programmed death ligand 1 (PD-L1). In total, 310 patients with advanced or metastatic urothelial carcinoma following progression on platinum-based chemotherapy were treated with atezolizumab on a single-arm phase II trial, and an exploratory analysis studying the association of mutation load with response was performed [18]. The overall objective response rate was 15% (95% CI: 11–19), and a subset of 150 patients underwent analysis with a panel of 315 cancer-related genes. The median mutation load in responders was 12.4 per megabase, which was significantly higher than the 6.4 per megabase value in non-responders ($P < 0.0001$). This association was independent of immune cell subgroup as stratified by PD-L1-positive immune cell percentage. Mutation load was also significantly associated with response in a similar exploratory analysis of atezolizumab in the first-line setting for advanced and metastatic urothelial carcinoma patients who were cisplatin-ineligible [19].