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EXPANDING TARGETED THERAPY OPPORTUNITIES IN BLADDER CANCER: THE ROLE OF COMPREHENSIVE GENOMIC PROFILING

Aim. Bladder cancer (BC) is a highly heterogeneous malignancy with limited response to standard therapies at advanced stages. This study intends to evaluate the actionable molecular profile of BC using a combined somatic and germline next-generation sequencing (NGS) approach to identify personalized targeted therapy options. **Methods.** We performed genomic profiling of 38 BC patients using the Ion GeneStudio S5 Plus System. DNA libraries were analyzed using a combined workflow of a somatic Cancer Hotspot and Custom Hereditary panels, followed by variant filtering and clinical tiering. **Results.** The NGS analysis showed pathogenic or likely pathogenic variants across 26 genes. The most frequently mutated gene was TP53, identified in 10 patients (26%). Direct clinical utility was demonstrated by activating the FGFR3 mutations in 7 patients (18%), which serve as susceptible targets for erdafitinib, an FDA-approved pan-FGFR inhibitor. Kinase domain mutations in ERBB2 (HER2) (p.Asp769Tyr, p.Val777Leu) were found in 1 patient, showing possible benefit from anti-HER2 antibody-drug conjugates such as trastuzumab or disitamab. Hyperactivation of the PI3K/AKT/mTOR pathway was driven by PIK3CA variants (4 patients), AKT1 mutation, and PTEN alteration, showing potentially therapeutic options such as inavolisib, alpelisib, and capivasertib. Mutations in TSC1 (4) and TSC2 (1) lead to constitutive mTORC1 activation, justifying an individualized approach with mTOR inhibitors like everolimus or temsirolimus. Furthermore, 10 patients harbored variants in the homologous recombination repair genes (BRCA1/2, CHEK2, BRIP1, NBN, RAD50), providing a rationale for PARP inhibitor use within the concept of BRCAness. We identified variants in the mismatch repair genes (MSH6, MSH3, PMS2, MUTYH) in 6 individuals; if a dMMR/MSI-H phenotype is confirmed, these patients are candidates for pembrolizumab immunotherapy. **Conclusions.** Overall, comprehensive genomic profiling identified clinically actionable alterations in 71% of the cohort. This includes 18% of patients eligible for FDA-approved targeted therapy (FGFR3-altered), alongside an additional 53% harboring investigational therapeutic targets. These findings demonstrate the high clinical utility of NGS testing for effective treatment stratification in bladder cancer.

Keywords: NGS, bladder cancer, targeted therapy.

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