Potential Role for Targeted Therapy in Muscle-Invasive Bladder Cancer

Lessons from the Cancer Genome Atlas and Beyond

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KEYWORDS

• Urothelial carcinoma • Whole-genome sequencing • Mutation analysis • Prognosis • Clinical trials • Targeted therapy

KEY POINTS

- Efforts of The Cancer Genome Atlas (TCGA) project and other studies have greatly advanced our understanding of genomic alterations associated with muscle-invasive bladder cancer.
- Alterations in tyrosine kinase receptors, intracellular signaling pathways, cell cycle regulators, molecular chaperones, and mediators of angiogenesis and immune response can influence bladder cancer progression and act as therapeutic targets.
- Recent whole-genome profiling studies have identified biomarker panels that can predict prognosis and may be used to identify patients who need more aggressive therapy.
- Combining surgical advances, novel targeted therapeutics, and companion theranostics represents the new paradigm for personalized treatment of muscle-invasive bladder cancer.

GENOMIC LANDSCAPE OF BLADDER CANCER

Urothelial carcinoma of the bladder (UCB) has now been recognized as evolving and progressing through at least 2 distinct molecular pathways.[1,2] Nearly 70% of low-grade noninvasive papillary tumors, which generally tend to recur locally but rarely invade and metastasize, show constitutive activation of the receptor tyrosine kinase (RTK)-Ras pathway, with activating mutations in *HRAS* and fibroblast growth factor receptor 3 (*FGFR3*) genes.[3] In contrast, carcinoma in situ (CIS) and invasive tumors show frequent alterations in the *TP53* and retinoblastoma (*RB*) genes and pathways.[4]

Although previous efforts using targeted molecular analyses have elucidated several pathways that are important for bladder tumorigenesis and cancer progression, the advent of high-throughput profiling strategies has enabled comprehensive characterization of genomic alterations for the disease.[5] Several studies have used this approach to identify genomic loci associated with the risk of developing UCB and characterizing clonal development across various disease stages.[6,7]

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Leveraging advances in whole-genome expression profiling, next-generation sequencing, microarray analysis, and methylation arrays, The Cancer Genome Atlas (TCGA) project has comprehensively profiled 131 high-grade muscle-invasive UCBs.[8] This effort has cataloged genes that are mutated in a significant proportion of bladder cancers, several of which were not previously reported (**Table 1**). The analysis suggested that the burden of genetic alterations in UCB is similar to lung adenocarcinoma and squamous cell carcinoma and melanoma, but more than in other adult malignancies.[9]

TCGA results indicated that there were 302 exonic mutations, 204 segmental alterations in genomic copy number, and 22 genomic rearrangements on average per sample. Genes with statistically significant levels of recurrent somatic mutation were identified by Mutation Significance (MutSig) and the Catalogue of Somatic Mutations in Cancer (COSMIC) databases.[9–11] Whole exome sequencing revealed a median somatic mutation rate of 5.5 per megabase, with 49% of samples having *TP53* mutations; 12% of samples had *FGFR3* mutations that mostly affected known kinase-activating sites.

In addition to documenting genomic alterations, such efforts also have identified molecular subtypes of urothelial carcinoma. These efforts complement and extend previous studies that used pathway-based and global profiling approaches to categorize UCB based on histologic differentiation and prognosis.[12–14] Integrated mRNA, microRNA, and protein data analysis by TCGA identified 4 distinct subsets of muscle-invasive UCB.[8] A "papillary-like" cluster was enriched for tumors with papillary morphology, *FGFR3* overexpression, and associated mutations, amplifications, and translocations resulting in fusion with *TACC3* that result in constitutive activation, as previously reported by Williams and colleagues.[15] Tumors harboring these translocations may be particularly sensitive to FGFR3-targeted therapy. The remaining tumors shared genomic alterations similar to those of other tumor types, including lung adenocarcinoma, squamous cell cancers, and breast cancer. For example, 2 clusters showed features similar to luminal A breast cancer, with high expression of ERBB2 and estrogen receptor 2 (*ESR2*) signaling signature, indicating potential targets for hormone-based therapies, such as tamoxifen and raloxifene. The signature of another "basal/squamous-like" cluster resembled basal-like breast cancers and squamous cell carcinomas with overexpression of primitive cytokeratins (such as *KRT5*, *KRT6A*) and epidermal growth factor receptor (*EGFR*). First reported by Volkmer and colleagues,[13] such categorization into basal, luminal, and squamous subtypes based on molecular taxonomy also has been independently suggested by other groups.[16,17] Taken together, these observations suggest that effective targeted therapies used for other organ site cancers may provide similar benefit in patients with muscle-invasive UCB.

APPLYING GENOMICS TOWARD PROGNOSIS

Currently, clinical and histopathologic staging are the most commonly used prognostic tools for management of UCB. Statistical techniques, such as recursive partitioning and principal component analyses, have leveraged the prognostic potential of individual clinical variables to develop decision models that can predict oncological outcomes before cystectomy, thereby identifying patients who may require more aggressive therapy.[18,19] Clinical nomograms incorporate parameters such as age, gender, tumor and nodal stages, and histologic grade to estimate the risk of disease recurrence following radical cystectomy for invasive bladder cancer.[20,21] Such multivariate models can provide more accurate stratification of risk compared with single clinicopathologic prognosticators, although they are limited by the predictive power of their component clinical metrics.

Over the past 2 decades, several studies have identified individual molecular markers that are independently prognostic in UCB.[4] Such initial profiling investigations have characterized alterations in individual markers or across defined functional pathways. Several such studies concluded that a combination of markers was more prognostic than individual molecular alterations alone.[22] However, the low-to-medium throughput interrogation strategies, such as immunohistochemistry (IHC) and quantitative polymerase chain reaction, used in early investigations limited their discovery potential and were biased toward reexamining previously identified markers.[5] More recent efforts have used high-throughput unbiased approaches to interrogate coding regions of the entire genome to identify molecular panels that can distinguish disease subgroups that differ in their prognosis.[23,24] Using custom cDNA microarrays, Blaveri and colleagues[25] identified 24 unique genes based on prediction analysis that had a 78% success rate for classifying muscle-invasive bladder tumors into good and bad prognosis groups based on overall survival. Similar approaches have been used by other groups to identify multimarker gene panels that are prognostic for cancer-specific and overall survival in muscle-invasive UCB.[26–28]