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Targeted therapies in the treatment of urothelial cancers

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Abstract

Progress has been slow in systemic management of locally advanced and metastatic bladder cancer over the past 20 years. However, the recent approval of immunotherapy with atezolizumab and nivolumab for second-line salvage therapy may usher in an era of more rapid improvement. Systemic treatment is suboptimal and is an area of substantial unmet medical need. The recent findings from The Cancer Genome Atlas project revealed promising pathways that may be amenable to targeted therapies. Promising results with treatment using vascular endothelial growth factor inhibitors such as ramucirumab, sunitinib or bevacizumab, and human epidermal growth factor receptor 2 targeted therapies, epidermal growth factor receptor inhibitors, and fibroblast growth factor receptor inhibitors, are undergoing clinical trials and are discussed later.

Keywords: Urothelial cancer; Angiogenesis; HER2; Targeted therapy

Introduction

Bladder cancer is a major cause of morbidity and mortality nationwide. In 2016, 76,960 patients were diagnosed with bladder cancer and 16,390 projected to die of bladder cancer [1]. Although chemotherapy as a systemic treatment for bladder cancer has gained acceptance in the metastatic as well as neoadjuvant setting, chemotherapy's beneficial effects are limited [2]. Among all bladder cancers, urothelial cancers make up the most of the histologic subtype of bladder cancer, which will be the topic of discussion for this review. Immunotherapy has played a role in bladder cancer for decades. The use of vaccine bacillus Calmette-Guérin has been a standard approach in localized bladder cancers for more than 3 decades. Recently, the landscape of treatment has changed with the United States Food and Drug Administration (FDA) approval of atezolizumab as a second-line systemic option in metastatic bladder cancer in 2016 for those who have progressed on platinum-based therapies [3], along with approval of Nivolumab in 2017 [4], with pembrolizumab also showing very promising findings [5]. However, there is increasing interest in the use of molecularly targeted therapies (see Fig.) especially in the era of better precision medicine to target cancers, especially since response to chemotherapy may be short lived with clonal evolutionary changes that results from selective pressure [6]. Early studies have shown that efforts to apply molecularly targeted therapies for those with true molecular targets may have better outcomes than for those who do not and there is increasing genomic heterogeneity that appears to make bladder cancer amenable to targeted agents [7]. Furthermore, findings from The Cancer Genome Atlas (TCGA) project has brought to light unique molecular pathways that are aberrant in bladder cancers that could offer new approaches for specific targeting [8]. In addition, finding genomic alterations in varying settings, even smoking, may help further delineate the different outcomes of patients [9].

Findings of the TCGA

TCGA project was funded and supervised by the National Cancer Institute's Center of Cancer Genomics and National Human Genome Research Institute with the overarching goal of genomically characterizing and sequencing different tumor types. The bladder cancer TCGA project first reported on a comprehensive analysis

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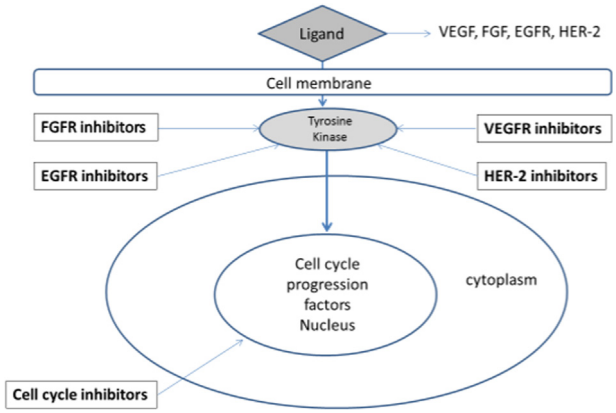

Fig. Potential targets in urothelial carcinoma. Different ligands (VEGF, FGF, EGFR, and HER-2) bind the receptor in the extracellular domain resulting in dimerization and initiation of signaling cascade leading to cell proliferation, angiogenesis, and growth. (Color version of the figure available online.)

of clinical, genomic, and pathologic data involving 131 muscle-invasive chemotherapy-naïve bladder cancers in 2014 [8,10].

The samples for TCGA analysis was obtained from 19 tissue sources of 131 previously untreated chemotherapy-naïve bladder cancers with peripheral blood samples in 18 patients as well as adjacent normal appearing histological samples adjacent to tumors in 23 patients. Analyses included sequencing data, DNA copy number, protein expression, mRNA and microRNA expression, DNA methylation, gene fusions, somatic mutations, and protein expressions. Four distinct subsets or expression clusters of urothelial carcinoma were identified via integrated analyses of mRNA, miRNA, and protein data, which formed clusters I to IV. Only 3 of these 4 clusters were fully characterized. Cluster I was particularly enriched with fibroblast growth factor receptor (FGFR) 3 alterations, expression or miRNA expression, seen in papillary histology and tissue morphology. Clusters I and II showed high expression of human epidermal growth factor receptor (EGFR) 2 (HER2) and estrogen receptor beta ESR2, which is reminiscent of HER2-positive breast cancers. Cluster III on the other hand, showed high expression of epithelial cell markers and stem cell progenitor lineage genes, which showed variant squamous histology akin to basal-like breast cancers or lung or head and neck tumors. In addition, whole-exome sequencing identified nearly half showed TP53 mutations, which were inactivating in 76% of the samples. TP53 mutations were found to be mutually exclusive of amplification and overexpression with MDM2, since MDM2 is a protein coding gene that encodes for a nuclear-localized E3 ubiquitin ligase that targets p53 for degradation. Inactivating retinoblastoma (RB1) mutations were also seen which was mutually exclusive with Cyclin Dependent Kinase Inhibitor 2A (CDKN2A) deletions. RB1 mutations were seen in approximately 13% of TCGA samples, and significant mutations were noted also in CDKN1A, CDKN2A, and Cyclin D 3 (CCND3). Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) mutations occurred in approximately 20% of samples whereas FGFR3 mutations occurred in around 12% of tumors. Truncating mutations in tuberous sclerosis complex 1 (TSC1) occurred in approximately 8% of tumors. The TCGA analyses also yielded novel findings of genes not previously known to be mutated in urothelial cancers such as the epigenetic regulatory MLL2 (myeloid/lymphoid or mixed-lineage leukemia protein 2 gene, CCND3, Ras Homolog Family Member A (RHOA) although there were 9 genes not also previously reported in other cancer types. Other interesting findings include mutations occurring in the RXRA (retinoid X nuclear receptor alpha) in the ligand-binding domain, which involves constitutive activation in genes responsible for lipid adipogenesis. There was also a very high frequency of chromatin remodeling gene alterations and receptor tyrosine kinase pathway alterations found. Regulation of the antioxidative stress pathway was seen in the form of missense mutations in nuclear factor, erythroid 2 like 2 (NFE2L2) in 8% of tumors as well as in 15 out of 16 tumors with excision repair 2 (ERCC2) deleterious missense mutations, a nucleotide excision repair gene pathway. In addition, other efforts at comprehensive genomic profiling has revealed also common clinically relevant genomic alterations include CDKN2A (34%), FGFR3 (21%), PIK3CA (20%), and ERBB2 (17%) [11]. These findings herald the opportunities for targeting different pathways in urothelial cancer, with efforts at updating the TCGA analyses currently underway.

Efforts to include biomarkers to further define genomic aberrations in bladder cancer are underway. The use of circulating cell-free DNA has shown a wide range of promise though practical applicability still remains unclear. A small number of patients ($n = 29$) showed the most common mutation to be TP53, BRCA, FGFR2, and EGFR [12,13]. The advent of genomic-based assays have also revolutionized clinical trial conduct in this disease such that targeted treatment such as in the NCI-MATCH trial has propagated testing and treatment. In the field of urothelial cancer, one such trial is BISCAY, which is an open-label, randomized, multi-drug, biomarker-directed, Phase 1b Study in those with muscle-invasive bladder cancer (NCT02546661). This trial randomizes patients into 5 different arms including a monotherapy arm with AZD4547 (an FGFR inhibitor), a combination of AZD4547 with durvalumab, another arm with durvalumab + olaparib, another with AZD1775 with durvalumab, durvalumab monotherapy and the durvalumab + Vistusertib (an oral inhibitor of the mammalian target of rapamycin, mTOR). Increasing recognition of DNA repair gene defects also may pave the way for ultimately delineating excellent responders to chemotherapy or targeted therapies that may predict adequate responses that may preclude the need for radical cystectomy [14,15].