Review

Elevating the Horizon: Emerging Molecular and Genomic Targets in the Treatment of Advanced Urothelial Carcinoma

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Abstract

Despite recent advances in the identification of genomic alterations that lead to urothelial oncogenesis in vitro, patients with advanced urothelial carcinomas continue to have poor clinical outcomes. In the present review, we focus on targeted therapies that have yielded the most promising results alone or combined with traditional chemotherapy, including the antiangiogenesis agent bevacizumab, the human epidermal growth factor receptor 2 antibody trastuzumab, and the tyrosine kinase inhibitor cabozantinib. We also describe ongoing and developing clinical trials that use innovative approaches, including dose-dense scheduling of singular chemotherapy combinations, prospective screening of tumor tissues for mutational targets and biomarkers to predict chemosensitivity before the determination of the therapeutic regimen, and novel agents that target proteins in the immune checkpoint regulation pathway (programmed cell death protein 1 [PD-1] and anti-PD-ligand 1) that have shown significant potential in preclinical models and early clinical trials. New agents and targeted therapies, alone or combined with traditional chemotherapy, will only be validated through accrual to developing clinical trials that aim to translate these therapies into individualized treatments and improved survival rates in urothelial carcinoma.

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Introduction

Urothelial carcinoma is the fifth most common cancer in the United States. From the Surveillance, Epidemiology, and End Results data, it has been estimated that approximately 75,000 new cases will have been reported in 2014. Owing to the relatively slow advances in the search for effective treatments, the outcomes for patients with muscle-invasive and metastatic urothelial carcinomas are worse than those for patients with other types of solid tumors. Seventy percent of urothelial carcinomas are not muscle invasive, for which local treatments can be effective. However, 15% to 20% of patients with non–muscle-invasive disease will progress to muscle-invasive urothelial carcinoma. At diagnosis, 25% to 30% of patients will present with muscle-invasive disease, 25% of whom already harbor lymph node metastases not visible on conventional imaging. Moreover, approximately 5% will present with distant metastatic urothelial carcinoma at diagnosis. In patients with locally advanced or metastatic disease, the 5-year survival rate is approximately 15%.[1] Currently, the only approved treatments of locally advanced or metastatic disease are cisplatin-based chemotherapy combinations. Although almost 50% of patients respond to cisplatin combined with either gemcitabine (GC) or with methotrexate, vinblastine, and doxorubicin (MVAC), the duration of response is around 7 months.[2] Patients who develop a relapse after initial chemotherapy generally have a poor response to subsequent treatments and thus a poor prognosis.[3] Although the need is clearly urgent for systemic treatments of metastatic urothelial carcinoma, only a few cytotoxic therapy combinations have been approved by the U.S. Food and Drug Administration (FDA) for first-line treatment, and none has been approved for second-line treatment. No new agent has been approved for the treatment of metastatic urothelial carcinoma in the past 30 years. Among the greater than 120 FDA-approved anticancer agents, only a small percentage has even been tested against urothelial carcinoma.

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Barriers to Development of Effective Therapies for Urothelial Carcinoma

Multiple factors have impeded the progress in developing effective treatments of urothelial carcinoma. First, many large randomized trials of urothelial carcinoma have closed prematurely owing to poor patient accrual, the reasons for which appear to be complex.[4-7] A significant number of patients with urothelial cancer are ineligible for cisplatin because of a performance status of $\geq$ 2, reduced creatinine clearance, hearing loss, peripheral neuropathy, and New York Heart Association Class III heart failure.[8] Although these comorbidities present a challenge when assessing patients for clinical trial eligibility, renal insufficiency is especially significant, owing to its high prevalence in this patient population. A retrospective analysis found that 24% to 52% (depending on the formula used to calculate the creatinine clearance) of patients with urothelial cancer had a glomerular filtration rate of less than 60 mL/min/1.73 m^2 after cystectomy,[9] which would compromise eligibility for many trials. Although urothelial cancer is a disease of the elderly (median age, 73 years),[10] no evidence has supported an association between chronologic age and greater toxicity with cisplatin-based chemotherapy.[8] Furthermore, although lung cancer has a similar age distribution (median age, 70 years),[11] this fact does not appear to compromise accrual into lung cancer trials and therefore should not be a factor in determining eligibility. Owing to poor accrual, investigators tend to design small, single-arm, phase II trials, the results of which are not likely to change the treatment paradigm, as demonstrated by a 2013 analysis of ongoing trials for metastatic urothelial carcinoma.[12] Based on these observations, the Bladder Cancer Advocacy Network Clinical Trials Working Group released a report emphasizing the urgent need for communication and collaboration among investigators to overcome this major barrier to developing effective treatments of urothelial carcinoma.[12]

Biology of Urothelial Carcinoma

Another obstacle to improved treatments of urothelial carcinoma is a lack of understanding of how this disease develops and progresses. Historically, the lack of effective therapies might also have contributed to poor accrual into clinical trials. In the past decade, investigators have made a tremendous effort to address this issue. The most detailed analysis, published in 2014, was performed by the Cancer Genome Atlas Research Network.[13] In that analysis, 131 samples of muscle-invasive bladder carcinoma were investigated for DNA copy number changes, somatic mutations, messenger RNA and microRNA expression, protein and phosphorylated protein expression, DNA methylation, transcript splice variation, gene fusion, viral integration, pathway perturbation, and clinical correlates to reveal the molecular landscape of urothelial carcinoma. The data collected identified several currently targetable genomic changes that are also supported by other research groups as important pathways in urothelial oncogenesis (ie, the phosphoinositide 3-kinase [PI3K]/protein kinase B [AKT]/mammalian target of rapamycin [mTOR] and receptor tyrosine kinase [RTK]/RAS pathways, including human epidermal growth factor receptor [HER2], v-erb-b2 avian erythroblastic leukemia viral oncogene homolog 3 [ERBB3], and fibroblast growth factor receptor 3 [FGFR3]) (Table 1).[13-15] The analysis also found alterations in novel pathways such as cyclin-dependent kinase (CDK) inhibitor 2A/CDK4/cyclin D1 and several epigenetic changes for which many new targetable agents are being developed.[13] Multiple clinical studies in the past decade have tested the efficacy of targeting several of these pathways in urothelial carcinoma, as summarized in comprehensive reviews.[14-16] In the present review, we highlight the most promising results from trials using targeted agents, report on ongoing clinical trials, and discuss novel trial designs for the treatment of muscle-invasive or metastatic urothelial carcinoma.

Increasing the Efficacy of Cytotoxic Treatments of Urothelial Carcinoma

First-line Therapy and Mechanisms of Resistance

Cisplatin, the backbone of combination chemotherapy for urothelial carcinoma, acts by forming inter- and intrastrand crosslinks in DNA, resulting in DNA damage and consequent cell death.[17] Preclinical studies have identified the mechanisms of resistance to cisplatin as decreased influx or increased efflux of drug, glutathione or metallothionein conjugation, drug detoxification, and DNA repair.[17] Although several key players underlying resistance to cisplatin have been identified,[17-19] none of these discoveries has led to a therapeutic application. The genes associated with chemoresistance could potentially become biomarkers for predicting the treatment response. For example, somatic mutations of excision repair cross-complementation group 2 (ERCC2), a gene involved in the nucleotide excision repair pathway, have been shown to correlate with cisplatin sensitivity.[20] Also, activating missense mutations of ERBB2 are significantly more prevalent in tumor tissue from complete responders to neoadjuvant chemotherapy.[21]

While investigating the clinical applications for the cellular mechanisms underlying cisplatin resistance, researchers have attempted to increase the efficacy of currently approved cisplatin-based combinations. The gompertzian kinetics of tumor growth posit a negative correlation between tumor growth and tumor size,[22] suggesting that administering cytotoxic chemotherapy in shorter intervals could maximize its effect by attacking the tumor while it is small and fast growing. Dose-dense scheduling is supported with growth factors to increase the tolerability of this potentially toxic regimen. A randomized phase III trial compared a traditional MVAC regimen to dose-dense MVAC with growth factor support.[23] The response rates with the dose-dense regimen improved (from 50% to 64%), along with tolerability; however, these positive outcomes did not culminate in a survival benefit. In another phase III trial, dose-dense GC was found to be equivalent to dose-dense MVAC in terms of survival, was associated with fewer instances of neutropenic fever, and was better tolerated.[7] However, it should be noted that this latter trial randomized fewer patients than anticipated owing to poor accrual and administrative issues.[7]

Neoadjuvant Therapy

To capitalize on their efficacy and tolerability, dose-dense regimens were also investigated in the neoadjuvant setting, where platinum-based treatment of resectable urothelial carcinoma has shown a survival benefit.[24-26] It was recently reported that when