Future Directions and Targeted Therapies in Bladder Cancer

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KEYWORDS

• Urothelial carcinoma • Biologic agents • Therapeutic targets • Systemic therapy

KEY POINTS

- Current systemic therapy for metastatic urothelial carcinoma yields a median survival of 12 to 15 months in the first-line setting and only 6 to 8 months in the salvage setting.
- The Cancer Genome Atlas project has provided important insights regarding molecular tumor tissue alterations in bladder cancer.
- Emerging data provide promise for a potential role for programmed death 1 and programmed death ligand 1 pathway inhibitors, phosphatidylinositol 3 kinase/mammalian target of rapamycin pathway inhibitors, fibroblast growth factor receptor 3 inhibitors, antiangiogenic agents, epigenetic modulation, and stem cell drivers in selected patients.
- Novel clinical trial designs guided by predictive biomarkers based on preclinical data may accelerate therapeutic advances.

INTRODUCTION

Despite the high response rates seen in the first-line metastatic setting with cisplatin-based chemotherapy regimens for metastatic urothelial carcinoma (UC), the duration of response is brief and salvage systemic therapy with available agents (vinflunine, taxanes) is marginally active.[1–4] The limited efficacy of currently used first-line

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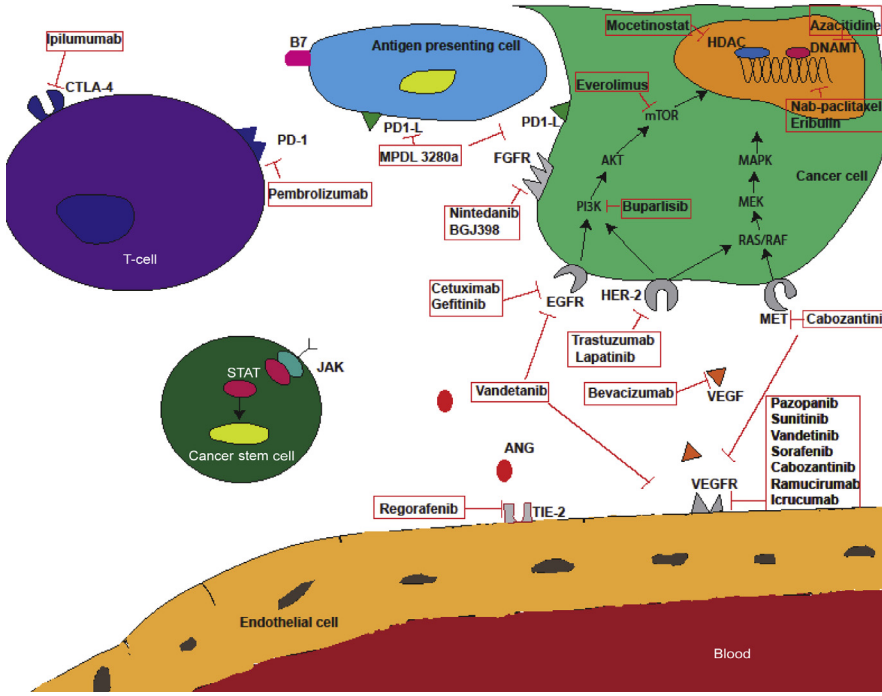

Fig. 1. Key molecular drivers of UC and potential therapeutic targets. ANG, angiopoietin; APC, antigen-presenting cell; DNMT, DNA methyltransferase; EGFR, epidermal growth factor receptor; FGFR, fibroblast growth factor receptor; HDAC, histone deacetylase; PD, programmed death; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor.

regimens and meager results with salvage chemotherapy translate to poor median survivals of only 12 to 15 months and 6 to 8 months, respectively. In addition, a large proportion of patients, especially elderly patients, do not receive chemotherapy or are ineligible for cisplatin-based combination chemotherapy because of poor performance status, renal dysfunction, and comorbidities, and show poor outcomes with carboplatin-based therapy.[5–8] The settings of perioperative systemic therapy, combined modality therapy with concurrent radiation, and bacillus Calmette-Guérin (BCG)–resistant non–muscle-invasive bladder cancer (NMIBC) also have suboptimal outcomes. Although no major advances have occurred for the systemic therapy for UC in more than 2 decades, better understanding of tumor biology has identified multiple potential therapeutic targets. This article discusses future directions and highlights emerging promising systemic agents for the treatment of UC.

POTENTIAL NOVEL THERAPEUTIC TARGETS

The Cancer Genome Atlas (TCGA) project recently provided multiple novel insights, although a single dominant tumor driver was not evident (**Fig. 1**).[9] Chromatin regulatory genes were more frequently mutated in muscle-invasive bladder cancer than in other common malignancies, suggesting a role for targeting epigenetic pathways. Most (76%) tumors harbored an inactivating mutation in 1 or more of the chromatin regulatory genes, and 41% had at least 2 such mutations. Recurrent mutations were observed in genes involved in cell-cycle regulation, chromatin regulation, and kinase signaling. RNA sequencing revealed 4 expression subtypes, including a