Targeted Therapy in Advanced Bladder Cancer
What Have We Learned?

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KEYWORDS

• Urothelial carcinoma • Targeted therapy • Small molecule inhibitors • Next-generation sequencing • Angiogenesis • MAPK pathway • PI3K/Akt/mTOR pathway

KEY POINTS

- Clinical trials of targeted agents in urothelial carcinoma have not displayed a significant improvement in response or outcome compared with chemotherapy.
- None of these trials have incorporated prospective sequencing to identify predictive biomarkers of response to therapy.
- Predictive biomarkers are crucial for identifying patients most likely to obtain benefit from targeted agents.
- Basket clinical studies will allow targeted agents to be assessed across tumor types based on the presence of a specific genetic biomarker.

BACKGROUND

Urothelial carcinoma (UC) is the second most common genitourinary malignancy in the United States, with an estimated 74,690 new cases and 15,580 estimated deaths in 2014.[1] For locally advanced or metastatic UC, first-line cisplatin-based chemotherapy results in an overall response rate (ORR) of 50% to 70%, a median progression-free survival (PFS) of 7 to 9 months, and median overall survival (OS) of 12 to 15 months.[2] The doublet of gemcitabine plus cisplatin (GC) offers similar survival rates to that of the 4-drug regimen of methotrexate, vinblastine, doxorubicin, and cisplatin with a median survival of 14.0 months (95% confidence interval [CI], 12.3–15.5 months) versus 15.2 months (95% CI, 13.2–17.3 months), respectively. Although these survival outcomes outstrip the estimated 6-month survival rates observed before these regimens, advances are indisputably needed.[2] The addition of paclitaxel to GC chemotherapy improved response rates but did not show a significant improvement in median survival and resulted in increased toxicity,[3] whereas the use of dose-dense therapies have to date not resulted in improvements in OS.[4] These results, coupled with the success of targeted agents in other cancer types such as renal cell carcinoma (RCC), non–small cell lung cancer (NSCLC), and chronic myelogenous leukemia, have driven the search to define a role for targeted therapies in advanced UC.

GENETIC ALTERATIONS IN UROTHELIAL CARCINOMA

Sequencing of UC tumors initially identified 2 distinct mutation patterns, which correlated with tumor grade. Low-grade papillary tumors were characterized primarily by oncogenic mutations in the fibroblast growth factor receptor 3 (*FGFR3*; ~70%), *HRAS* (30%–40%), and *PIK3CA* (~10%)

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genes.[5] Conversely, invasive lesions harbored frequent loss of function alterations in tumor suppressor genes, including *TP53* and *RB1*.[6,7] The Cancer Genome Atlas (TCGA) has since provided a more granular insight into the landscape of genetic alterations within muscle-invasive UC.[8] Despite a high mutation burden, many alterations can be organized into well-known signaling pathways and canonical cellular functions against which inhibitors have been approved by the US Food and Drug Administration (FDA) in other cancer types or are currently under investigation.[9] These pathways primarily include the receptor tyrosine kinase (RTK) pathway, comprised of the epidermal growth factor receptor (EGFR) family of receptors, FGFR3, and numerous others, and the phosphoinositide 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathway. Additionally, UC is characterized by a high frequency of alterations within cell cycle regulatory genes, including *CDKN2A* deletion and *CCND1* amplification. Chromatin modifiers such as *KDM6A*, *KMT2D*, and *ARID1A* represent another class of genes commonly mutated in this disease. Finally, angiogenesis is thought to play a key role in UC growth and metastatic spread, and components of this signaling axis are also altered in UC. Most targeted therapy trials performed thus far in UC have investigated RTK and angiogenic signaling inhibitors and mTOR inhibitors. These studies are the focus of this discussion and are outlined in **Table 1**.

RECEPTOR TYROSINE KINASE SIGNALING INHIBITORS

Epidermal Growth Factor Receptor Signaling

EGFR (Erbb1) is a 170-kDa transmembrane RTK critically important for the regulation of cell proliferation, invasion, and metastasis in preclinical models of UC.[10] Activation of the EGFR-tyrosine kinase (TK) stimulates both the MAPK and PI3K/Akt/mTOR signaling pathways. Additional members of the ErbB family of receptors also involved in mitogenic signaling via the MAPK pathway include HER2 and HER3. EGFR and HER2 have both been examined as potential targets in UC. In the bladder TCGA, comprised of untreated muscle-invasive specimens, MAPK pathway alterations include EGFR amplification (9%), HER2 amplifications and mutations (9%), and HER3 mutations (6%).

Gefitinib

Gefitinib is an oral, selective EGFR TK inhibitor currently used in EGFR-mutant NSCLC patients and has activity against EGFR-expressing UC cell lines.[11] Gefitinib was evaluated in a phase II trial in metastatic UC patients who did not respond to one prior chemotherapeutic regimen. In the 31 patients enrolled, the median PFS was 2 months with one confirmed partial response (PR).[12] Pretreatment biopsies were required for retrospective evaluation of EGFR expression, although overexpression was not an inclusion criterion. The partial responder's tumor harbored 2+ EGFR expression; 8 of 15 patients showed primary progression (2 to 3+ EGFR expression). No correlation was noted between EGFR staining and response; additionally, this study was designed before the observation that EGFR mutations correlate with gefitinib sensitivity in NSCLC.

The Cancer and Leukemia Group B conducted a multicenter phase II study (CALGB 90102) evaluating the addition of gefitinib (500 mg/d) to GC in untreated patients with advanced UC.[13] All patients received 6 cycles of GC plus gefitinib, and those with objective responses or stable disease (SD) were continued on maintenance gefitinib until progression. An ORR of 42.6% was observed with 7 complete responses (CR) and 16 PRs. The median OS was 15.1 months; the median time to progression was 7.4 months. Grades 3 to 4 hematologic toxicity were seen in 22% patients (n = 12). Nonhematologic grade 3 toxicities included fatigue (20%), emesis (24%), diarrhea (14%), and rash (11%). Based on these results, the addition of gefitinib does not seem to improve response rate or survival compared with chemotherapy alone. Notably, patients were not screened for EGFR overexpression or mutation before trial enrollment.

Erlotinib

Erlotinib, another EGFR TK inhibitor, was tested in 20 patients with histologically confirmed muscle-invasive UC in the neoadjuvant setting for 4 weeks before radical cystectomy.[14] Seven patients (35%) with clinical T2 disease had their disease downstaged to non-muscle-invasive bladder cancer, and 5 patients (25%) had no residual disease, comparing favorably with historical rates of less than pT2 disease after transurethral resection or neoadjuvant chemotherapy, although the lack of a comparator arm in this study limits the ability to draw definitive conclusions. Treatment was well tolerated with rash the most common side effect observed in 15 patients (75%). Five patients who achieved pT0 responses within the bladder exhibited the acneiform rash known to correlate with response to EGFR TK inhibition in NSCLC and colon cancers. Although patients were not preselected based on EGFR mutations or amplification, tumors are being retrospectively analyzed