Review

New Directions for Biologic Targets in Urothelial Carcinoma

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Abstract

Urothelial carcinoma remains an important oncologic problem with significant morbidity and mortality. This article provides an overview of the current status of treatment of urothelial carcinoma, with an update on current trials and recent American Society of Clinical Oncology abstracts. As an alternative to focusing on the metastatic setting, we take a broad look at drug development to date, as it spans from early disease to advanced disease in the context of emerging molecular data. This approach allows us to show that each stage involves key considerations based on emerging evidence regarding molecular biology, stage-specific novel endpoints, and rational patient selection that may help further trial designs in the future. Key issues, such as neoadjuvant versus adjuvant perioperative chemotherapy, approaches to salvage second-line therapy in the metastatic setting, and treatment of elderly and cisplatin-ineligible patients, are discussed. New paradigms in clinical research, including novel endpoints, upfront rational patient selection, biomarkers, and trial design, are also addressed. *Mol Cancer Ther; 11(6); 1226–35. ©2012 AACR.*

Introduction

Urothelial carcinoma, which can affect the bladder, ureters, or renal pelvis, is the sixth most common cancer overall, accounting for 70,000 new cases and 18,000 deaths in North America in 2010 (1). Urothelial carcinoma has 3 main presentations: nonmuscle-invasive disease, muscle-invasive disease, and metastatic disease. Conventional management has reached a therapeutic plateau at all stages of the disease, but recent advances in molecular biology have identified new therapeutic targets that may translate into better treatments and improved outcomes. This article provides an overview of the current treatment options and ongoing and reported clinical trials from PubMed, the Clinical Trials.gov database, and American Society of Clinical Oncology abstracts. Key issues, such as neoadjuvant versus adjuvant chemotherapy, salvage second-line options, and treatment of cisplatin-unfit patients, as well as aspects of clinical trial design (e.g., patient selection, biomarkers, and novel endpoints), are also discussed.

Nonmuscle-Invasive Disease

Approximately 70% of newly diagnosed cases of urothelial carcinoma are nonmuscle-invasive urothelial carcinoma (NMIUC; previously called superficial disease,

which incorrectly implies nonaggressive disease). NMIUC is a heterogeneous group of cancers with a markedly diverse prognosis, including Ta (papillary), T1 (invades the submucosa), and Tis [carcinoma *in situ* (CIS)] cancers. Whereas low-grade Ta tumors frequently recur and infrequently progress to muscle-invasive disease, high-grade Ta, T1, and Tis tumors often progress and have worse outcomes. NMIUC is managed conservatively by transurethral resection with adjuvant intravesical therapy for patients with high-risk features, such as high-grade, large, or multifocal tumors; CIS; or recurrent tumors (2). Although a number of intravesical agents, such as mitomycin C and doxorubicin, have been tried, immunotherapy with Bacille Calmette-Guerin (BCG) is the most commonly used treatment. BCG eradicates residual tumor and reduces the risk of recurrence, but up to one third of patients will still experience recurrence, requiring repeat transurethral resection and sometimes cystectomy, which is associated with considerable morbidity (3).

Trials of newer chemotherapies, targeted therapies, and immune-based approaches are under way (Table 1). For BCG-refractory patients, early results from a phase I/II study of intravesical nab-paclitaxel, a novel albumin-bound form of paclitaxel, are encouraging (4). Sunitinib, an oral VEGF tyrosine kinase inhibitor (TKI) that has been approved in metastatic kidney cancer, and the antisense oligonucleotide OGX-427 to HSP27 are 2 targeted therapies that are also being studied in NMIUC (5, 6). Immunomodulatory approaches, such as using a combination of interferon and BCG or a mycobacterial cell wall DNA complex (MCC), are also being explored (7, 8). MCCs exert their anticancer activity by inducing anticancer cytokines and having a direct proapoptotic effect on cancer cells (9).

Perhaps the greatest potential for developing new treatments lies in the understanding that NMIUC may actually be 2 distinct diseases (low-grade and high-grade), each

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Table 1. Current active phase II and III trials in NMIUC

Agent(s)	Setting	Trial[a]	Correlates
DTA-H19/PEI	Phase IIb, second line	NCT00595088	
Sunitinib	Phase II, second line	NCT01118351	CTCs, Tregs, angiogenic markers
MCC	Phase II/III	NCT00406068	
BCG ± gefitinib	Phase III	NCT00352079	
Intravesicular nab-paclitaxel	Phase I/II	NCT00583349	

Abbreviations: CTC, circulating tumor cell; Treg, regulatory T cell.
[a]ClinicalTrials.gov registry number.

with its own morphology, molecular profile, and biologic behavior. Low-grade papillary tumors are often multifocal, rarely progress, and are associated with mutations in the fibroblast growth factor receptor 3 (FGFR3) pathway leading to constitutive activity via downstream *Ras* signaling pathways (10). FGFR3 is an attractive therapeutic target in these cancers because 60% of mutations occur at a single hotspot that is amenable to screening. Both tyrosine kinase inhibition with the FGFR TKI dovitinib and shRNA knockdown of *S249C* (the most common FGFR3 mutation) have shown preclinical inhibition of cell proliferation in low-grade cancers (11, 12). In contrast, high-grade tumors (commonly flat tumors, CIS, or occasionally papillary tumors) have increased invasive potential and show inactivation of the tumor suppressor genes retinoblastoma (*RB*) and *p53*. Mechanisms for *p53* inactivation include direct mutation or alteration of *p53*-interacting proteins, such as MDM2. MDM2 is an E3 ligase responsible for ubiquitin-dependent degradation. It is overexpressed in ~30% of patients with urothelial carcinoma, and is linked to high-grade tumors. Several agents aimed at restoring *p53* function either directly or through their interaction with modifiers such as MDM2 are in development and may prove to be beneficial for high-grade disease (13).

NMIUC provides an example of how we can achieve rational drug development by matching clinical and molecular characteristics to specific targeted therapies. For low-grade disease due to FGFR3 mutations, the FGFR TKIs may be particularly effective, even if they lack activity in advanced disease. Similarly, as *p53*-reactivating agents proceed into phase II studies, enriching clinical trials for high-grade disease and *p53*-inactivating mutations may increase our chance of seeing a benefit with these new agents. This shift in trial design, where molecular phenotype is used to select patients, may ultimately lead to greater success in drug development and better outcomes.

Muscle-invasive disease

Muscle-invasive urothelial carcinoma (MIUC) may present as progression from NMIUC or as *de novo* disease (14). Despite radical cystectomy and bilateral pelvic lymphadenectomy, up to 50% of patients will still experience recurrence and may die of their disease. Five-year survival rates for organ-confined (T2) disease are 68% but drop to 25%–30% with extravesical extension. Attempts to improve survival have focused on the use of perioperative (neoadjuvant or adjuvant) chemotherapy, but many issues remain to be resolved, including the optimum timing for chemotherapy, the ideal chemotherapy regimen, and how best to personalize perioperative treatment.

Adjuvant chemotherapy

The main advantage of chemotherapy given after surgery or adjuvant chemotherapy is that there is no delay to definitive local therapy, and complete pathologic staging is available before systemic treatment is administered. The biggest disadvantages are the delay to systemic treatment against micrometastatic disease, inability to assess chemosensitivity, tolerability in the postoperative period, and patient refusal. To date, most large adjuvant chemotherapy trials have been small, underpowered, stopped early, or had variability in the chemotherapy regimens used. Furthermore, the allotted treatments often were not received, which made it difficult to determine the benefit of adjuvant chemotherapy with any precision.

Two of 6 completed randomized trials have shown a survival benefit. Skinner and colleagues (15) randomized 91 patients to cystectomy plus adjuvant cisplatin, cyclophosphamide, and doxorubicin or cystectomy alone, and showed a prolonged disease-free survival (DFS) at 5 years of 51% for adjuvant chemotherapy versus 34% for no adjuvant chemotherapy ($P = 0.011$), but no difference in overall survival (OS). A trial by Lehmann and colleagues (16) in which pT3-pT4a and/or N+ patients were randomized postcystectomy to methotrexate, vinblastine, Adriamycin, and cisplatin (MVAC); methotrexate, vinblastine, epirubicin, and cisplatin (MVEC); or no chemotherapy was stopped after an interim analysis showed a progression free-survival (PFS) of 43.7% versus 13.0% ($P = 0.002$) and OS of 26.9% versus 17.4% ($P = 0.069$), supporting adjuvant chemotherapy. Both of these trials were small and underpowered, and they had methodological flaws. Investigators in the Advanced Bladder Cancer Meta-Analysis Collaboration analyzed 491 patients in 6 cisplatin-based adjuvant chemotherapy randomized trials and found a 25% relative reduction in risk of death and 9% improvement in 3-year OS from adjuvant chemotherapy, but the overall quality of the trials was a concern (17). A pooled analysis of 5 trials also showed a significant

benefit from adjuvant chemotherapy in both OS [response rate (RR), 0.74; 95% CI, 0.62–0.88; $P = 0.001$] and DFS [RR, 0.65; CI 0.54–0.78; $P < 0.001$ (18)]. Taken together, current results suggest a benefit from adjuvant chemotherapy in at least delaying disease progression and possibly improving OS, but further data are clearly needed.

Unfortunately, definitive adjuvant chemotherapy trials continue to be hampered by poor accrual and early closures. Preliminary results from an Italian trial comparing adjuvant gemcitabine and cisplatin (GC) with observation in 194 postcystectomy pT2 grade 3, pT3-4, N0-2 patients showed no difference in DFS or OS at 2 years, but it closed early due to poor accrual (19). Similarly, the Spanish Oncology Genitourinary Group study of 4 cycles of adjuvant paclitaxel, gemcitabine, and cisplatin (PGC) versus observation in resected pT3-4 and/or pN+ disease also closed early. At a 30-month median follow-up, OS was significantly prolonged in the PGC arm (median not reached, 5-year OS: 60%) versus observation (median 26 months; 5-year OS: 31%; $P < 0.0009$). DFS ($P < 0.0001$), time to progression (TTP, $P < 0.0001$), and disease-specific survival ($P < 0.0002$) were also superior in the PGC arm (20). The EORTC 30994 phase III trial comparing immediate versus deferred adjuvant chemotherapy (MVAC, high-dose MVAC, or GC) in pT3-4– or node-positive patients also closed early as a result of poor accrual (21). A Cancer and Leukemia Group B study of sequential doxorubicin and gemcitabine followed by paclitaxel and cisplatin versus GC alone also ended early, highlighting the challenges of conducting adjuvant chemotherapy trials (22).

The cause of poor accrual to adjuvant chemotherapy trials is likely multifactorial. One issue is the significant variability in standard practices among centers, and in a center where adjuvant chemotherapy and a particular chemotherapy regimen is routinely used, randomizing patients to no adjuvant chemotherapy or to an alternate chemotherapy regimen may not be acceptable. Choosing and balancing centers for adjuvant chemotherapy trials according to their own standard practice may be one strategy to improve accrual. Another issue is that many patients have comorbidities or renal dysfunction, making them ineligible for trials. This needs to be considered both in terms of sample size and in the inclusion/exclusion criteria to permit generalization of final results. Patient refusal for adjuvant chemotherapy could also be an issue, underscoring the need for a multidisciplinary approach in which perioperative chemotherapy and the option of clinical trials are discussed at the time of cystectomy and not after. Finally, education of both physicians and patients about the poor outcomes in MIUC with cystectomy alone, and the critical importance and need for well-conducted clinical trials to guide practice and inform the decision as to who should receive perioperative chemotherapy may also translate into better accrual to adjuvant chemotherapy trials.

To address the issue of selecting patients to receive adjuvant chemotherapy, Stadler and colleagues (23) conducted a trial in which 114 patients with pT1-2, N0, *p53*-positive ($\geq 10\%$ immunoreactivity) disease were randomized to 3 cycles of adjuvant MVAC or observation. Although this study was halted early after an interim futility analysis could not confirm the prognostic or predictive value of *p53*, the authors clearly made a new and important step forward in urothelial carcinoma by exploring the idea of tailoring treatment according to molecular phenotype. This has already been done in breast cancer; for example, investigators can use the Oncotype DX genomic test to examine a 21-gene panel and determine the likelihood of both recurrence and benefit from chemotherapy. The challenge in urothelial carcinoma will be to establish which genes or panel of genes will have prognostic and predictive value.

Neoadjuvant chemotherapy

In contrast to adjuvant chemotherapy, neoadjuvant chemotherapy has the advantage that systemic therapy against micrometastatic disease is initiated earlier, tumor and pathologic responses can be assessed *in vivo*, tumor downstaging may lead to bladder-sparing surgery, and patients often tolerate treatment better preoperatively. The main disadvantage is the lack of full pathology at the time of neoadjuvant chemotherapy, and patients who are chemoresistant may progress during neoadjuvant chemotherapy, making them ineligible for surgery, although early reassessment of neoadjuvant chemotherapy response could reduce this risk.

Several randomized neoadjuvant chemotherapy trials have been reported; however, these trials were small, used inadequate chemotherapy, closed early, or had limited follow-up. The largest phase III study randomized 976 T2 grade 3, T3/T4a N0/X patients to 3 cycles of CMV or no chemotherapy followed by cystectomy and/or radiotherapy. After a median 8 years follow-up, recently updated results of this trial showed that neoadjuvant CMV reduced the risk of death by 16%, increasing 10-year survival 30% to 36%, and median survival (MS) 37 to 44 months (24, 25). Similar results were reported in a trial of 307 patients with T2-4a (60% had T3 or T4a) who were randomized to 3 cycles of neoadjuvant MVAC and cystectomy or cystectomy alone. Neoadjuvant MVAC reduced the risk of death by 25% (HR 0.75; 95% CI, 0.57–1.0; $P = 0.06$), with an MS of 77 months versus 46 months with surgery alone. Of note, 38% of patients who received neoadjuvant chemotherapy were disease free at cystectomy ($P < 0.001$), and 85% with pT0 disease were alive at 5 years (26). Similar pathologic RRs were seen with dose-dense MVAC (ddMVAC; given every 2 weeks, with growth factor support). ddMVAC had comparable toxicity and a shorter delay to definitive surgery. A meta-analysis of 2,688 individual patients treated in 10 randomized neoadjuvant chemotherapy trials showed no benefit from single-agent cisplatin, but combination cisplatin regimens showed a significant OS benefit (HR = 0.87; 95% CI, 0.78–0.98; $P = 0.016$), a 13% decrease in risk of death, and a 5% absolute OS benefit at 5 years (45%–50%)

versus surgery alone (12). A smaller meta-analysis of 2 Nordic trials also showed an OS benefit, which was greater in T3 compared with T2 disease. Together, these studies provide compelling evidence that neoadjuvant chemotherapy followed by cystectomy should be considered as a standard approach to optimize outcomes in MIUC.

Despite evidence that neoadjuvant chemotherapy confers a 5% survival benefit, the use of neoadjuvant chemotherapy remains universally low (27, 28). Reasons for this low uptake may include physicians' desire to wait for the final pathology report, concerns about delaying surgery, and the belief that the magnitude of benefit from neoadjuvant chemotherapy is trivial compared with its toxicities. Patient-related factors may include advanced age, comorbidities, renal dysfunction, preference for surgery, and fear of chemotherapy. Resource issues, such as the availability of medical oncologists, familiarity with neoadjuvant chemotherapy approaches, and the challenge of scheduling operating room time after neoadjuvant chemotherapy, may also play a role. Strategies to increase the use of neoadjuvant chemotherapy may not only improve outcomes but may also aid in accrual to several ongoing neoadjuvant trials in which novel therapies may be more optimally be evaluated.

Neoadjuvant clinical trials testing new combinations and targeted therapies are under way, with the added benefit of having tissue available for correlative studies (Table 2). A phase II study of neoadjuvant gemcitabine, carboplatin, and nab-paclitaxel showed a pathologic complete response (pCr) rate of 30% and no invasive disease in 54% of the patients (29). In terms of targeted therapy, there is interest in the use of angiogenesis inhibitors. Although such inhibitors have been disappointing in advanced disease, earlier evaluation or combination with chemotherapy may lead to improved results. Small-molecule TKIs that block phosphorylation of the vascular endothelial growth factor receptor (VEGFR) intracellular tyrosine kinase domain, and monoclonal antibodies against the extracellular domain of the receptor or VEGF ligand have been evaluated. Two TKI trials, one with GC plus sunitinib and another with GC plus the TKI sorafenib, are ongoing with pCr as a key endpoint (30, 31). In another trial of MVAC with the VEGF antibody bevacizumab, investigators are assessing angiogenesis and downstream pathways using 2-color terminal deoxynucleotidyl transferase–mediated dUTP nick end labeling (TUNEL) and microvessel density, which could be very informative (32). Patients who received a fairly intense regimen of neoadjuvant ddMVAC plus bevacizumab, and radical cystectomy followed by adjuvant bevacizumab plus paclitaxel had increased surgical complications, but 27% had no residual invasive disease (33). The epidermal growth factor receptor (EGFR) TKI erlotinib showed a 30% pT0 rate when given for 4 weeks before cystectomy (34), and a similar phase 0 study with lapatinib, a dual EGFR/Her 2 inhibitor, is currently recruiting participants (ClinicalTrials.gov identifier NCT01245660). A trial of dasatinib, an oral multi-BCR/ABL and Src family TKI, is also currently ongoing (ClinicalTrials.gov identifier NCT00706641).

The neoadjuvant approach provides the ideal paradigm for research by allowing for an *in vivo* assessment of tumor response to novel treatments, and the availability of pre- and post-treatment tumor tissue for studying both predictive/prognostic markers and functional imaging correlates. A growing body of evidence suggests that pCR is a surrogate marker for survival in urothelial carcinoma. In a

Table 2. Current active phase II trials in potentially resectable Urothelial carcinoma

Agent(s)	Setting	Trial[a]	Correlates
Gem/carbo/paclitaxel	Phase II, pot resect	NCT00136175	P53, RB, p21
Gem/carbo/nab-pacli	Phase II, neoadj	NCT00585689	
Sunitinib	Phase II, neoadj	NCT00526656	VEGFR-1, -2, PDGF-R, Treg
Gem/cis/bev (neoadj) and pacli/bev (adj)	Phase II, periop	NCT00268450	pT0 cystoscopy, surgery
MVAC + bev	Phase II, neoadj	NCT00506155	Assess angiogenesis and downstream pathways, including 2-color TUNEL, phospho-receptor, and microvessel density
Erlotinib	Phase II, neoadj	NCT00749892	
Sunitinib	Phase II, adj in patients treated with neoadj	NCT01042795	
Dasatinib	Phase II neoadj	NCT00706641	
Gem/cisplatin/sunitinib	Phase II, neoadj	NCT00847015	

Abbreviations: adj, adjuvant; bev, bevacizumab; carbo, carboplatin; gem, gemcitabine; nab-pacli, nab-paclitaxel; neoadj, neoadjuvant; PDGF, platelet-derived growth factor; pot resect, potentially resectable.
[a]ClinicalTrials.gov registry number.

retrospective analysis of the SWOG 8710 trial, Sonpavde and colleagues (35) showed that residual disease after neoadjuvant chemotherapy and incomplete node dissection (<10 nodes removed) were linked to worse prognosis. Both clinical stage at diagnosis and pathologic stage at radical cystectomy were predictive of OS. A similar analysis of the 2 Nordic trials also showed the importance of pathologic downstaging with regard to outcome. These efforts may help us predict which patients are likely to benefit from systemic therapy or identify those who can opt out of potentially toxic, ineffective chemotherapy. Overall, neoadjuvant clinical trials may represent the best opportunity to move the field forward by elucidating tumor response and resistance at both clinical and molecular levels.

Bladder preservation in muscle-invasive disease

In patients who are unfit for or decline cystectomy, several bladder-sparing approaches (e.g., radiation alone) have been explored, but local recurrence rates are high and 5-year OS is poor. The addition of cisplatin concurrently with radiation therapy has been shown to improve disease control and is used in many centers (36). A recent trial of concurrent 5FU-mitomycin and radiation showed that this combination resulted in better local control and improved PFS, but did not affect OS (37). Although there are no prospective randomized trials of concurrent chemoradiation (CRT) versus cystectomy, the Medical Research Council (MRC) trial did show better outcomes with 3 cycles of CMV before radiation therapy or cystectomy (25). A phase II trial evaluating concurrent weekly gemcitabine with radiation in 50 patients with T2-3 disease showed good tolerability and a CR rate of 88%, 3-year cancer-specific survival of 82%, and OS of 75% (38). Bladder-sparing approaches focusing on tumor biology, such as radiation with p53-targeted agents or hypoxia-modifying agents, are under study. Most commonly, a trimodality approach consisting of maximal transurethral resection and concurrent CRT with radiosensitizing chemotherapy is offered, followed by close clinical and cystoscopy follow-up.

Metastatic urothelial carcinoma

Despite aggressive management of localized urothelial carcinoma, up to 50% of patients will develop metastatic disease, and another 20% will have metastatic disease at presentation. Cisplatin-based combination chemotherapy is the standard of care for fit patients with adequate renal function. Although RRs to first-line cisplatin-based chemotherapy approach 50%, these responses are rarely durable, and not all patients are eligible for cisplatin-based chemotherapy. Overall life expectancy remains a dismal 14 months. MVAC was the first regimen to be approved for metastatic urothelial carcinoma with better efficacy than single-agent cisplatin (39), but it was associated with a 3% to 4% toxic death rate. In an attempt to improve on MVAC, investigators examined ddMVAC, which was better tolerated but had similar efficacy (40). A

simpler, 2-drug regimen of GC showed comparable efficacy, RR (49.4% vs. 45.7%), and OS (13.8 months vs. 14.8 months) to MVAC, but it had a better safety profile, was easier to administer, and was more cost-effective, leading to its widespread approval and use (41, 42). MVAC is still used in young or fit patients because long-term followup of the study initially reported by Loerher and coworkers did show a 3.7% cure rate in the MVAC arm (39, 43). Outcomes have not been improved by the addition of a third agent to standard GC. Although paclitaxel in combination with GC in a phase I/II study showed an RR of 78%, the phase III trial showed lower RRs of 57% and a nonsignificant 3-month improvement in MS (44).

Unfortunately, many patients are not candidates for cisplatin due to comorbidities or renal dysfunction; however, this is a fairly heterogeneous group of patients, which makes it difficult to design clinical trials. To standardize the definition of cisplatin-unfit patients, Galsky and colleagues (45) proposed a consensus definition that includes (i) Eastern Cooperative Oncology Group performance status ≥ 2, (ii) creatinine clearance < 60 mL/min, (iii) Common Terminology Criteria for Adverse Events (CTCAE) grade ≥ 2 hearing loss, and (iv) CTCAE grade ≥ 2 neuropathy. Carboplatin is sometimes used in this setting, but studies have been limited and outcomes seem to be suboptimal. In patients with kidney dysfunction, a first-line trial of eribulin, a unique microtubule-targeting agent, is under way (46). Eribulin showed good tolerability and an encouraging RR of 38% in the first-line setting (47), and it is also being studied in combination with GC versus GC alone in a randomized phase II trial. The first randomized phase II/III trial in cisplatin-unfit patients with advanced urothelial carcinoma showed similar poor outcomes (OS of 9.3 vs. 8.1 months) with GC and methotrexate/carboplatin/vinblastine (M-CAVI), but more severe toxicity with M-CAVI (21.2%), indicating that this remains an area of unmet need (48).

In the second-line setting, there are no effective, well-tolerated treatment options. To date, the only drug that has been tested in a phase III trial against best supportive care is the microtubule-targeted agent vinflunine, which showed an overall RR (ORR) of 8.6%, PFS of 3.0 months, and OS of 6.9 months. Although it is approved in Europe, vinflunine has not been widely adopted due to significant toxicity, including neutropenia, fatigue, anemia, and constipation (49). The most commonly used second-line agents are the taxanes, which yield an RR of only 10% but have tolerability and a lack of nephrotoxicity. A second-line trial of the novel taxane nab-paclitaxel showed encouraging results, with an RR of 32% and OS of 10.6 months (50). The activity of nab-paclitaxel may be related to expression of SPARC, an albumin-binding protein found in high-grade urothelial carcinoma that facilitates chemotherapy delivery, but correlative studies are needed to confirm such a relationship. Nab-paclitaxel was well tolerated, and neurotoxicity was not a significant issue despite prior treatment with cisplatin. On the basis of its tolerability and efficacy, further study of

nab-paclitaxel in second-line urothelial carcinoma is clearly warranted. Trials to assess nab-paclitaxel in the first-line setting against GC or in cisplatin-unfit patients could also be considered. The only other single agent with encouraging results to date is pemetrexed, with an RR of 28% and a median OS of 9.6 months, although a smaller trial did not support those results (51).

In summary, the current standard therapy for advanced urothelial carcinoma is relatively toxic and cisplatin-based, rendering many patients ineligible for both standard therapy and trials investigating drug combinations that are designed as "standard plus investigational agent" regimens. Several ongoing trials are assessing targeted agents as single agents and in combination with or as alternatives to standard therapy (Table 3).

Anti-VEGF Therapy

Angiogenesis inhibition has emerged as an attractive strategy in urothelial carcinoma, where VEGF expression has been linked to tumor progression and prognosis (52).

Although preclinical studies suggest a benefit, clinical studies have shown only modest activity (53). Sunitinib has been evaluated in a first-line trial in cisplatin-unfit patients, and in 4 second-line and beyond single-agent trials. Investigators are conducting a first-line trial of GC with sunitinib, and an interesting trial of maintenance sunitinib after stable disease or response to first-line chemotherapy (54). Sorafenib is a TKI that blocks cellular proliferation via the ERK pathway and angiogenesis via the VEGF pathway. A first-line trial in chemonaïve patients showed no ORs, a TTP of 1.9 months, and MS of only 5.9 months, consistent with second-line findings (55, 56). A study of GC plus sorafenib showed significant toxicity (57). Toxicity was also an issue in a trial of GC plus bevacizumab: venothromboembolism rates were 16% to 21%, necessitating dose reduction or discontinuation (58). A phase III CALGB randomized study of GC with or without bevacizumab is ongoing, but accrual has been slow (59). Pazopanib, a second-generation oral TKI, is inactive; however, correlative studies including VEGFR and soluble VEGFR levels, as well as positron emission tomography (PET) imaging, may be quite informative (60,

Table 3. Current active phase II trials in metastatic Urothelial carcinoma

Agent(s)	Setting	Trial[a]
Gem/carbo/sorafinib	Phase II, chemonaïve	NCT00461851
Gem/sdcis/sorafinib	Phase II, chemonaïve	NCT00714948
Sunitinib	Phase II, platinum ineligible	NCT01118039
Sunitinib	Phase II, platinum ineligible	NCT00578526
Tesetaxel	Phase II, second line	NCT01215877
Gem/cis + sunitinib	Phase II, first line	NCT01089088
Eribulin	Phase Ib/II	NCT01126749
Everolimus ± paclitaxel	Phase II, first line	NCT01215136
Gem/cis ± cetuximab	Randomized phase II	NCT00645593
Gem/cisplat/eribulin	Phase Ib/II, chemonaïve	NCT01126749
Ixabepilone	Phase II, second line	NCT00021099
Kinesin spindle protein inhibitor	Phase II, second line	NCT00661609
Pralatrexate	Phase II platinum and/or MTX R	NCT00722553
Tipifarnib	Phase II, chemonaïve	NCT00006376
Larotaxel/cis vs. gem/cis	Phase III, chemonaïve	NCT00625664
Nab-paclitaxel/gem/carbo	Phase II, chemonaïve	NCT00995488
Omidepsin	Phase II, second line	NCT00087295
Lonafarnib/gem	Phase II, second line	NCT00006351
Gem/cis ± bev	Phase III	NCT00942331
Pazop/vinflunine	Phase I/II, platinum R	NCT01265940
Pazop	Phase II, second line	NCT00471536
Pazop	Phase II, second line	NCT01031875
Paclitaxel/pazop	Phase II, second line	NCT01108055
Dovitinib	Phase II, second line	NCT00790426
Volasertib	Phase II, second line	NCT01023958
Gem/cis ± vandetanib	Randomized phase II, first line	NCT01191892
Docetaxel ± IMC-1121b or -18F1	Randomized phase II	NCT01282463

Abbreviations: bev, bevacizumab; carbo, carboplatin; gem, gemcitabine; MTX, methotrexate; R, resistant; sdcis, split dose cisplatin.
[a]ClinicalTrials.gov registry number.

61). A combination study of pazopanib and paclitaxel in first line is under way (62). Other negative trials include a second-line aflibercept (VEGF-trap) trial and a combination trial of vandetanib plus docetaxel (63). A 3-arm second-line trial of docetaxel as monotherapy compared with docetaxel with either the VEGFR2 antibody ramucirumab or the VEGFR1 antibody IMC-18F1 is ongoing (64). Although angiogenesis may be necessary for tumor progression, the relative inactivity of these drugs may suggest intrinsic resistance, redundancy of the angiogenic pathways, or tumor dependence on alternate pathways. There is ongoing research to better understand these factors as well as the role of tumor hypoxia in mediating resistance to antiangiogenic therapies.

mTOR Pathway Inhibitors

The mTOR/PI3K/AKT pathway is instrumental in coordinating cell growth. Alterations include reduced PTEN expression, increased mTOR expression, and PI3K mutations (65). Temsirolimus and everolimus are mTOR inhibitors that are being investigated in phase I and II trials in a first- and second-line setting, respectively, with incorporation of biomarkers for mTOR activity (66).

EGFR/HER2 Inhibition

The rationale for targeting the EGFR pathway has been its overexpression and correlation with stage and survival. Again, however, preclinical activity has not translated into clinically relevant activity. A phase II study of GC plus the TKI gefitinib showed an ORR of 36% and MS of 11.1 months, but there was excessive toxicity (67). A similar study of GC plus the monoclonal antibody cetuximab is also under way. Because HER2/neu overexpression is also seen, a first-line study of trastuzumab with PCG in HER2-positive, chemonaïve patients showed an RR of 70%, a median TTP of 9.3 months, and MS of 14.1 months, with reasonable tolerability (68). However, despite promising preclinical activity, the EGFR/HER2 TKI lapatinib failed to show activity in a second-line trial in unselected patients, indicating the importance of patient selection in the development of these targeted therapies (69).

Other Targeted Therapies

Bortezomib is a reversible inhibitor of the proteasome pathway. Despite preclinical activity and synergy with gemcitabine, it was shown to lack second-line clinical activity (70). Polo-like kinases (Plk) regulate cell-cycle progression and mitosis. Overexpression in urothelial carcinoma has been related to higher grade, tumor number, and positive urine cytology. The Plk inhibitor BI6727 is currently being evaluated in a second-line trial (ClinicalTrials.gov identifier NCT01023958). Preliminary results showed that nearly 50% of patients achieved either stable disease or partial response, and the trial is ongoing

(71). Dovitinib, an FGFR inhibitor, was evaluated in a trial that stratified second- or third-line patients based on the presence or absence of the FGFR3 mutation (ClinicalTrials.gov identifier NCT00790426). This trial faced challenges involving testing of mutation status and is now closed, with final results pending. Cell-cycle checkpoint pathways offer the potential to sensitize cancer cells to the DNA-damaging effects of chemotherapy and radiation. Chk1 and Chk2 kinases are activated as a response to DNA damage. Novel Chk kinase inhibitors offer an exciting new approach to cancer cell sensitization and may serve as adjuncts to novel targeted agents. Finally, new evidence suggests that insulin-like growth factor 1R (IGF-1R) has a role in motility and invasion of bladder cancer cell lines, and potentially may serve as a marker of invasive phenotype and biomarker for disease progression (72). Developers of drugs for bladder cancer will evaluate newer generations of targeted therapies and new targets, such as IGF, met, src, and histone deacetylase. Immunotherapeutic approaches, such as the peptide vaccine NY-ESO-1 and stem cell markers, are also in early stages of clinical development.

Future Directions

Urothelial carcinoma remains a challenging disease, with limited progress made over the last 3 decades. For patients with advanced disease who progress on or are ineligible for platinum-based therapy, options are limited and prognosis is generally poor. As our understanding of tumor biology increases and more targeted agents become available, the key will be to carefully design clinical trials that match tumor biology with targeted agents to maximize benefit.

Metastatic urothelial carcinoma has a highly variable prognosis, with MS ranging from 2 to 14 months. Researchers have identified a number of key prognostic factors (e.g., visceral metastases, poor performance status, and low hemoglobin) that can be used for prognostication as well as stratification for clinical trials (39, 73). Other emerging prognostic factors include prior response and time from last chemotherapy. The roles of *p53* and other potential markers of chemoresistance (e.g., excision repair cross complementation protein) are also being explored, but these agents have yet to find a place in standard clinical practice and have not been shown in prospective trials to be biomarkers that are capable of guiding therapeutic decision-making (23). To date, the majority of trial designs have been based on histologic patient selection, with biomarkers used only on an exploratory basis. Although ideal, patient preselection using biomarkers may impact negatively on power and sample size in a disease, where accrual to clinical trials can be challenging. It is also important to develop treatments for cisplatin-unfit patients and histologic subtypes (e.g., squamous carcinoma and adenocarcinoma) whose biology and prognosis differ from the more-common transitional cell cancers. However, for studies in these and other

subpopulations to be feasible, strong collaborations and multi-institutional trials will be needed.

Patient selection based on molecular phenotype may be essential to realize the benefits of new therapies. In NMIUC this may translate into evaluating FGFR3- or p53-targeting agents based on molecular profile, and in MIUC this may mean designing trials in the neoadjuvant setting to allow for *in vivo* assessments of response and correlative studies for biomarkers of response and survival. In patients with advanced urothelial carcinoma, preselection based on molecular phenotype has already been used in the trastuzumab and dovitinib trials. The COXEN project, which translates *in vitro* chemosensitivity profiles into drug discovery (74), and the ONCOMAP project for druggable targets (75) may all help to improve patient selection for both standard treatments and clinical trials. Fresh tissue biopsies, as opposed to archival tissue, may also better reflect tumor biology. Whenever tissue is available, consideration should be given to tumor banking, microarray analysis, and validation of predictive markers. One challenge to the development of biomarkers and druggable targets is that urothelial carcinoma is driven largely by loss of the tumor suppressor genes *p53*, *PTEN*, *RB*, and *p16*, requiring restoration of lost function versus gain of function, which can more easily be targeted.

Selection of trial endpoints is also important, especially in urothelial carcinoma, where historical controls are not available or inadequate. Randomized phase II designs may help reduce selection bias and allow better assessments of clinically relevant outcomes compared with single-arm phase II trials. Two-stage trial designs that permit early stopping for futility may also be beneficial in a setting where many agents have been shown to be ineffective or too toxic. In terms of endpoints, standard RRs applicable to cytotoxic agents may not apply to cytostatic targeted therapies where PFS, prolonged stable disease, and quality of life may be more informative. Surrogate endpoints may include MRI or novel functional imaging methods, such as F18 fluorodeoxyglucose and fluorothymidine PET. Finally, as patient populations increasingly become subdivided into molecular subtypes, collaborations will be necessary to meet accrual targets in a timely fashion.

Conclusions

Overall, this is a very exciting time in the field of urothelial carcinoma. Our increased understanding of molecular pathways, the availability of targeted therapies, advances in the correlative sciences and study design, and strong multidisciplinary collaborations have now come together. Urothelial carcinoma research has been recognized as a priority area by the National Cancer Institute, which will translate into increased funding and, most importantly, improved overall outcomes in this disease.

Disclosure of Potential Conflicts of Interest

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Molecular Cancer Therapeutics

New Directions for Biologic Targets in Urothelial Carcinoma

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