Review

Perioperative and Maintenance Therapy After First-Line Therapy as Paradigms for Drug Discovery in Urothelial Carcinoma

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Abstract

Perioperative chemotherapy provided to increase the chance of cure for localized disease and maintenance therapy for metastatic disease represent 2 distinct aspects of the urothelial cancer disease treatment spectrum. The ability to access both pre- and postchemotherapy tissue in the neoadjuvant setting provides important opportunities for translational research to test novel therapies and identify predictors of response to therapy. The maintenance setting may be more complex, and study design and endpoints need to be determined on the basis of the candidate drugs' mechanisms of action and toxicity.

Clinical Genitourinary Cancer, Vol. 13, No. 4, 302-8 © 2015 Elsevier Inc. All rights reserved.
Keywords: Adjuvant therapy, Maintenance therapy, Neoadjuvant chemotherapy, Targeted therapy, Urothelial cancer

Neoadjuvant Chemotherapy

The use of cisplatin-based neoadjuvant chemotherapy for patients with muscle-invasive urothelial cancer (UC) of the bladder (MIBC) is supported by level 1 evidence. However, the optimal regimen, duration of therapy, and patient population have not been defined.

MVAC

In SWOG 8710, a total of 317 patients with stage T2N0M0 to T4aN0M0 bladder cancer were randomized to receive MVAC (methotrexate 30 mg/m^2 days 1, 15, 22, vinblastine 3 mg/m^2 days 2, 15, 22, doxorubicin 30 mg/m^2 day 2, cisplatin 70 mg/m^2 day 2) for 3 cycles every 28 days followed by cystectomy compared to cystectomy alone.[1] Grade 3 and 4 toxicities were predominantly hematologic and gastrointestinal, as this study completed accrual before the routine use of modern antiemetic and granulocyte growth factor support. At a median follow-up of 8.7 years, the median survival for patients receiving chemotherapy and cystectomy was 77 months compared to 46 months for those undergoing cystectomy alone ($P = .05$). Patients with pathologic complete response (pCR) in either group experienced improved overall survival (OS) than those with any residual tumor at cystectomy. The rate of pCR in the chemotherapy arm was 38% compared to 15% in the cystectomy-alone arm, which was presumably achieved by vigorous preoperative transurethral resection of bladder tumor (TURBT). Downstaging and survival outcomes in this trial set the benchmark for subsequent neoadjuvant chemotherapy studies in MIBC.

Gemcitabine and Cisplatin

A study of patients with advanced or metastatic bladder cancer randomized to treatment with cisplatin and gemcitabine (GC) versus MVAC showed similar 5-year outcomes and improved toxicity.[2] Many have extrapolated this benefit of GC to the perioperative setting, making this the most commonly utilized neoadjuvant regimen in the United States.[3] An international multicenter retrospective analysis of 212 patients found that the 146 patients treated with GC had similar pCR rates to the 66 patients treated with MVAC (51 of whom received accelerated MVAC).[4]

Future neoadjuvant trials should prospectively evaluate the benefit of cisplatin and gemcitabine compared to other regimens.

Accelerated MVAC

Accelerated MVAC was found to have improved chemotherapy tolerance, drug delivery, and a trend toward relative reduction in the risk of progression and death in patients in patients with locally advanced unresectable and metastatic bladder cancer compared to traditional MVAC.[5] Accelerated MVAC consists of the same agents as the traditional MVAC regimen, but provided all over day 1 or 2 only with growth factor support. In 2 separate studies, patients

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Submitted: Nov 25, 2014; Revised: Mar 16, 2015; Accepted: Mar 18, 2015; Epub: Mar 26, 2015

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1558-7673/$ - see frontmatter © 2015 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.clgc.2015.03.003

with cT2-cT4a N0-N1 MIBC were treated with 3 cycles (Plimack et al[6]) or 4 cycles (Choueiri et al[7]) of neoadjuvant accelerated MVAC. Both studies met their primary endpoint of pathologic response. Of the 40 evaluable patients in the Plimack et al trial, 38% experienced pCR, with the disease of another 14% downstaged to non-MIBC. Of the 39 patients in the Choueiri et al study, 49% were downstaged to non-MIBC, 10 of whom had pCR. Both groups reported responses in patients with clinical N1 disease, suggesting that tumor biology and not clinical stage may predict response to neoadjuvant therapy. Both groups cited excellent tolerance to the accelerated MVAC regimen, with significantly fewer grade 3 or 4 toxicities than previously reported with MVAC. Chemotherapy was completed efficiently, with both groups reporting a median time to surgery significantly shorter than that described in prior neoadjuvant trials.

In combination with bevacizumab, Siefker-Radtke et al reported a pCR rate of 39% in 44 patients with high-risk bladder cancer (lymphovascular invasion cT3b, hydronephrosis, micropapillary features, or tumor in a diverticulum) and a 2-year OS of 75%.[8]

CMV

In a trial by the National Cancer Research Institute Bladder Cancer Clinical Studies Group, patients with T2-T4a N0/x UCB were randomized to CMV (methotrexate 30 mg/m^2 days 1 and 8, vinblastine 4 mg/m^2 days 1 and 9, cisplatin 100 mg/m^2 day 2 with folinic acid) every 21 days for 3 cycles before cystectomy or radiotherapy. At a median follow-up of 8 years, patients treated with neoadjuvant chemotherapy had a 16% reduction in the risk of death compared to patients in the no-chemotherapy arm (95% confidence interval [CI], 0.72 to 0.99, $P = .037$). The study was not powered to determine differences between outcomes in patients who underwent surgery, radiotherapy, or both.[9]

Ongoing Study

SWOG 1314—A Randomized Phase 2 Study of Co-Expression Extrapolation (COXEN) With Neoadjuvant Chemotherapy for Localized, Muscle-Invasive Bladder Cancer (NCT02177695)—was activated in 2014. It randomizes patients with newly diagnosed stage cT2-T4a N0 MIBC to either GC or accelerated MVAC. The primary objective of the study is to determine if gene expression profiling (COXEN score) obtained from transurethral biopsy specimens is prognostic of response to neoadjuvant chemotherapy. Table 1 outlines registered studies in muscle invasive urothelial cancer that are discussed in this manuscript.

Pathologic Response After Chemotherapy

pCR has been associated with survival in the neoadjuvant setting in UC. In randomized controlled trials of neoadjuvant chemotherapy with pCR as an endpoint, the rate of pCR is consistently higher with chemotherapy than in cystectomy-alone arms.[10] However, there is some debate in the literature as to whether providing neoadjuvant chemotherapy represents overtreatment because some patients will experience pT0 based on transurethral resection alone. In the SWOG 8710 trial, OS for patients who experienced pCR in the MVAC arm versus those in the cystectomy-alone arm was similar, although the study was not powered to detect a difference in this subgroup.[1] In a retrospective analysis of patients who received MVAC followed by cystectomy with negative surgical margins, achievement of pCR correlated with improved survival outcomes compared to those who had any residual noninvasive tumors (pa, pT1, carcinoma-in-situ). Patients with residual $P >$ T2 tumors or positive lymph nodes had significantly worse survival outcomes compared to those with pCR.[11] In a meta-analysis of 13 studies of 886 patients who underwent neoadjuvant chemotherapy and cystectomy, achievement of pCR despite the treatment arm was

Table 1 Clinical Trials for Muscle-Invasive Urothelial Cancer

Regimen	Phase	Estimated Enrollment	Status	Primary Endpoint	ClinicalTrials.gov
Neoadjuvant					
Accelerated MVAC or GC (testing COXEN)	Phase 2	184	Open	Prognostic value of treatment-specific COXEN score	NCT02177695
GC and pembrolizumab or gemcitabine alone and pembrolizumab (cisplatin ineligible)	Phase 1b–2	81	Pending	Phase 1b: safety, tolerability; phase 2: pathologic muscle-invasive response	NCT02365766
Adjuvant					
DN 2402 versus observation	Randomized phase 2	180	Completed accrual	OS	NCT01353222
MAGE-A3 + AS-15 versus placebo	Randomized phase 2	273	Open	DFS	NCT01435356
Maintenance					
GC and bevacizumab versus GC and placebo	Randomized phase 3	500	Completed accrual	OS	NCT00942331
Vinflunine versus best supportive care	Randomized phase 2	86	Completed accrual	PFS	NCT01529411
GC and ipilimumab	Phase 2	36	Completed accrual	OS	NCT01524991
Docetaxel and OGX 427 versus docetaxel	Randomized phase 2	200	Open	OS	NCT01780545

Abbreviations: DFS = disease-free survival; GC = gemcitabine and cisplatin; MVAC = methotrexate, vinblastine, doxorubicin, cisplatin; OS = overall survival; PFS = progression-free survival.
Source: ClinicalTrials.gov, accessed March 14, 2015.