

# Update on Perioperative Systemic Therapy for Urothelial Carcinoma

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**Abstract:** Level 1 evidence supports cisplatin-based neoadjuvant chemotherapy (NAC) in muscle-invasive urothelial bladder cancer (MIUBC). Recent data from small prospective trials with neoadjuvant immune checkpoint inhibitors are encouraging, but long-term follow-up is required. Randomized trials have failed to accrue a sufficient number of patients and have not demonstrated a survival benefit with adjuvant chemotherapy in MIUBC, but for those with high-risk features at surgery, adjuvant cisplatin-based therapy is appropriate. In upper tract urothelial carcinoma, several retrospective trials and one recent phase 2 prospective trial support the use of NAC, and a randomized trial with adjuvant chemotherapy demonstrated improved disease- and metastasis-free survival and a trend toward improved overall survival.

## Introduction

Historically, radical cystectomy without neoadjuvant chemotherapy (NAC) for muscle-invasive urothelial bladder cancer (MIUBC) has been insufficient to provide a cure for all patients. After radical cystectomy, distant metastases develop in 25% of patients with organ-confined tumors ( $\leq$ pT2 N0), 37% of those with non-organ-confined tumors ( $>$ pT2 N0), and 51% of those with positive lymph nodes.<sup>1</sup> Furthermore, given the limitations of preoperative staging in MIUBC, occult nodal metastases are revealed after radical cystectomy in a high percentage of patients (24%) with clinically staged lymph node-negative (N0) disease.<sup>1</sup> Therefore, surgery alone is insufficient to treat MIUBC.<sup>2</sup> In meta-analyses and prospective randomized trials, NAC with a cisplatin-based combination improves the overall survival (OS) of patients with MIUBC.<sup>3-9</sup> Despite this survival benefit, many patients continue to undergo radical surgery up front owing to both patient and clinician factors.<sup>10</sup> The data for adjuvant chemotherapy are less robust, with encouraging results in small phase 2 trials and retrospective analyses but without positive results in phase 3 trials. If NAC has not been administered, adjuvant chemotherapy is appropriate for patients with pT3 or pT4 disease and positive lymph nodes.<sup>11</sup>

In this review, we present the current evidence for perioperative therapy in MIUBC, discuss the biomarkers indicating response to

treatment, summarize the data for perioperative chemotherapy in upper tract urothelial carcinoma (UTUC), and review the recent data on neoadjuvant immune checkpoint inhibitors in bladder cancer. Finally, we discuss ongoing trials of bladder-sparing approaches based on response to NAC and biomarkers in patients with MIUBC.

## Neoadjuvant Chemotherapy in Bladder Carcinoma

According to the National Comprehensive Cancer Network (NCCN) guidelines, NAC is recommended for patients with T2 to T4 disease.<sup>11</sup> Several studies have demonstrated a clinical benefit of NAC vs up-front cystectomy in MIUBC. A combined analysis of 2 Nordic trials that included 620 patients compared NAC consisting of a platinum agent plus doxorubicin or methotrexate with surgery alone. This analysis showed a 5-year OS rate of 56% in the combined chemotherapy arm and of 48% in the surgery-only arm (hazard ratio [HR], 0.80; 95% CI, 0.64-0.95;  $P=.049$ ).<sup>3</sup>

In the landmark Intergroup study affiliated with the Southwest Oncology Group (SWOG), Eastern Cooperative Oncology Group (ECOG), and Cancer and Leukemia Group B (CALGB), 317 patients with T2-T4a N0 M0 disease were treated with 3 cycles of neoadjuvant methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) followed by radical cystectomy, or with surgery alone. The median survival was 77 months in the combination therapy group vs 46 months in the surgery-alone group ( $P=.06$ , 2-sided test).<sup>4</sup> The 5-year overall survival (OS) rate was 57% in the neoadjuvant group and 43% in the cystectomy-only group ( $P=.06$ , 2-sided test).

The Medical Research Council and the European Organization for Research and Treatment of Cancer conducted an even larger trial that included 976 patients with T2 grade 3 disease or T3-T4a N0-Nx M0 disease, who received 3 cycles of neoadjuvant cisplatin, methotrexate, and vinblastine (CMV) or local therapy alone (cystectomy or radiotherapy). This trial did not show a statistically significant benefit of chemotherapy for OS in the initial report.<sup>5</sup> However, after a median follow-up of 8 years, the 10-year survival rate was 36% in the chemotherapy arm vs 30% in the surgery-alone group (HR, 0.84; 95% CI, 0.72-0.99;  $P=.037$ ).<sup>6</sup>

Furthermore, 3 meta-analyses demonstrated an OS benefit in patients with MIUBC who received cisplatin-based chemotherapy vs radical cystectomy alone, with an absolute benefit of 5% to 8% across the 3 studies.<sup>7-9</sup>

### Gemcitabine/Cisplatin in the Neoadjuvant Setting

In the metastatic setting, gemcitabine plus cisplatin (GC) achieved OS and progression-free survival (PFS) similar

to those achieved with standard MVAC, with a superior safety profile.<sup>12</sup> This experience has been extrapolated to the neoadjuvant setting, with GC frequently used as NAC, but without any prospective clinical trial data to describe the efficacy of GC in MIUBC. An ongoing phase 3 trial (NCT01812369) is comparing GC vs dose-dense MVAC (DD MVAC) in the perioperative setting. However, a recent large retrospective analysis of more than 1100 patients with MIUBC showed that the rate of downstaging to non-muscle-invasive disease was higher with DD MVAC than with GC (52.2% vs 41.3%, respectively;  $P<.001$ ), and on adjusted analysis, downstaging was more likely with MVAC than with GC (odds ratio [OR], 1.84; 95% CI, 1.10-3.09), as was a complete response (OR, 2.67; 95% CI, 1.50-4.77).<sup>13</sup>

In 2 small retrospective chart reviews investigating GC in the neoadjuvant setting, the pathologic complete response (pCR) rates were 26% and 21% (Table 1).<sup>14,15</sup> Dose-dense modification of GC was evaluated in 2 recently reported prospective phase 2 trials.<sup>16,17</sup> In the study of Anari and colleagues, 31 patients with clinical stage T2-T4a N0-N1 M0 disease received 3 cycles of dose-dense gemcitabine and cisplatin (DD GC) followed by radical cystectomy. A pCR occurred in 10 patients (32%), and the tumors of 4 patients (13%) were downstaged to non-muscle-invasive disease.<sup>16</sup> Iyer and colleagues evaluated 46 patients with MIUBC, who received 6 cycles of DD GC. Downstaging to less than T2 N0 was achieved in 57% of the patients, with a 15% pT0 rate.<sup>17</sup> However, high rates of grade 3 and 4 adverse events were noted in both studies (35% and 37%), including significant vascular events leading to early closure of one of the studies.<sup>16,17</sup> Thus, excess toxicity has limited the usability of this regimen.

### Dose-Dense MVAC in the Neoadjuvant Setting

Several recent prospective phase 2 trials have used a dose-dense or accelerated variation of MVAC for improved outcome and reduced toxicity.<sup>18-20</sup> The pCR rate has ranged from 26% to 43% with DD MVAC, with the grade 3 and 4 toxicity rate ranging from 10% to 18%. Plimack and colleagues enrolled 40 patients with T2-T4a N0-N1 M0 MIUBC, who received 3 cycles of neoadjuvant accelerated MVAC. This trial showed a 38% pCR rate, and the rate of downstaging to less than pT2 disease was 14%.<sup>19</sup> Similarly, Choueiri and colleagues evaluated 39 patients with MIUBC, who were administered 4 cycles of DD MVAC followed by radical cystectomy. In this study, the disease of 49% of patients was downstaged to pT1 N0 M0 or lower. Grade 3 or higher toxicity was observed in 10% of patients.<sup>20</sup>

In summary, the standard of care in 2018 for NAC in MIUBC outside a clinical trial is DD MVAC or GC (Table 1).

**Table 1.** Selected Trials of Neoadjuvant Chemotherapy for Bladder Cancer With Gemcitabine/Cisplatin or Accelerated MVAC

Drugs	Gemcitabine/Cisplatin				Accelerated MVAC		
	Standard		Dose-Dense				
Study first author	Dash <sup>14</sup>	Tully <sup>15</sup>	Anari <sup>16</sup>	Iyer <sup>17</sup>	Blick <sup>18</sup>	Plimack <sup>19</sup>	Choueiri <sup>20</sup>
No. of pts	42	154	31	46	80	40	39
Prospective or retrospective	R	R	P	P	R	P	P
No. of cycles	4	4	3	6	3-4	3	4
No. of weeks	12	12	6	12	6-8	6	8
Percentage of pts with pCR (pT0)	26%	21%	32%	15%	43%	38%	26%
Downstaged to $\leq$ pT1	36%	46%	45%	57%	~61%	53%	49%
Median No. of days from start of NAC to surgery	138	120	65	~114+	75	68	~98
Rate of grade 3-4 AEs	NA	NA	35%	37%	NA	18%	10%
2-y PFS rate	64%	~68%	~68%	~76%	65%	78%	~47%
2-y OS rate	73%	~75%	~77%	~87%	77%	83%	<80%

AEs, adverse events; MVAC, methotrexate, vinblastine, doxorubicin, and cisplatin; NA, not available; NAC, neoadjuvant chemotherapy; No., number; OS, overall survival; P, prospective; pCR, pathologic complete response; PFS, progression-free survival; pts, patients; R, retrospective; y, year.

### ***Biomarkers of Response to Neoadjuvant Chemotherapy***

In addition to improving oncologic outcomes in this disease, the neoadjuvant setting is an optimal platform for the discovery of predictive biomarkers.

Using a prospective trial of 34 patients treated with neoadjuvant DD MVAC as a discovery set, Plimack and colleagues showed a correlation between genomic alterations in *ATM*, *RBI*, or *FANCC*, identified in the pre-NAC transurethral resection of bladder tumor (TURBT) specimen, and pathologic response (defined as  $\leq$ pT1 N0 M0 disease;  $P < .001$ ). The study also demonstrated better PFS ( $P = .0085$ ) and OS ( $P = .007$ ) in the biomarker-positive group, with a positive predictive value of 100% for response.<sup>21</sup> A subsequent validation set based on a separate trial of 24 patients treated with neoadjuvant DD GC confirmed a promising positive predictive value of 78% for the presence of 1 of these 3 markers in predicting a pCR.

At the same time, Van Allen and colleagues showed a correlation between somatic *ERCC2* mutations and a complete response to cisplatin-based chemotherapy in MIUBC.<sup>22</sup> As a follow-up, Liu and colleagues used pre-NAC samples from 62 patients with MIUBC in 2 clinical trials. All patients received 3 cycles of cisplatin-based chemotherapy. This analysis showed a better response and a statistically significant increase in OS in the patients with somatic *ERCC2* alterations.<sup>23</sup> Also, a higher number of genomic alterations correlated with a greater

probability of response to cisplatin-based NAC.<sup>21,22</sup> Taken together, these 4 mutations (*ATM*, *RBI*, *FANCC*, and *ERCC2*) may be viable tissue biomarkers to help identify patients with tumors more likely to respond to cisplatin-based chemotherapy, possibly enabling the selective implementation of bladder-sparing approaches.

On the basis of the preceding findings, at least 3 ongoing clinical trials are selecting patients for bladder preservation according to mutation profile and response to NAC.<sup>24-26</sup> The first 2 trials use neoadjuvant cisplatin-based chemotherapy alone (NCT02710734 and NCT03609216), and the third trial uses neoadjuvant cisplatin-based chemotherapy plus the programmed death 1 (PD-1) inhibitor nivolumab (Opdivo, Bristol-Myers Squibb; NCT03558087). In NCT02710734, patients begin with DD MVAC and a simultaneous mutational analysis of prechemotherapy TURBT tissue. When patients have one or more of the mutations that may sensitize them to NAC (ie, *ATM*, *RBI*, *FANCC*, or *ERCC2*) and lead to a good response, post-NAC TURBT analysis and imaging are done, and if no residual disease is seen, these patients have the option of choosing bladder preservation and entering active surveillance.

### ***Role of Neoadjuvant Immunotherapy in Bladder Cancer***

Several small prospective trials were designed to test the

**Table 2.** Neoadjuvant Immunotherapy in Bladder Cancer: Early Results of Phase 2 Trials

Study First Author	Powles <sup>27</sup> (ASCO 2018)	Necchi <sup>28</sup> (JCO 2018)	Gao <sup>29</sup> (ASCO 2018)	Hoimes <sup>30</sup> (ESMO 2018)
Drug	Atezolizumab	Pembrolizumab	Durvalumab/tremelimumab	GC/pembrolizumab
No. of pts	69	50	12	40
Stage, TNM	T2-T4	T2-T3b, N1 allowed (4%)	T2-T3b, high-risk features	T2-T4a
Percentage of pts cisplatin-ineligible	100%	8%	100%	0%
Duration of immunotherapy	2 cycles (6 wk)	3 cycles (9 wk)	2 cycles (10 wk)	4 cycles (12 wk)
Safe <sup>a</sup>	Yes	Yes	Yes	Yes
Percentage of pts with pCR (pT0)	29%	42%	50% (of 6 pts who completed cystectomy)	40%
Biomarker data presented	Yes	Yes	Yes	Yes

<sup>a</sup> Per overall assessment of the investigators.

ASCO, American Society of Clinical Oncology annual meeting; ESMO, European Society for Medical Oncology annual meeting; GC, gemcitabine and cisplatin; JCO, *Journal of Clinical Oncology*; No., number; pCR, pathologic complete response; pts, patients; wk, weeks.

hypothesis that neoadjuvant immunotherapy, like chemotherapy, in patients with MIUBC could lead to downstaging (Table 2). ABACUS (Preoperative MPDL3280A in Transitional Cell Carcinoma of the Bladder), a phase 2 trial that included 69 patients with T2-T4 N0 M0 cisplatin-ineligible MIUBC, investigated neoadjuvant therapy with 2 cycles of the anti-programmed death ligand 1 (anti-PD-L1) checkpoint inhibitor atezolizumab (Tecentriq, Genentech), given at a dose of 1200 mg intravenously every 3 weeks. Of the 69 patients in this study, 14 (20%) received only 1 cycle (8 because of adverse events).<sup>27</sup> The pCR rate was 29% at the interim analysis, and the tumors of 39% were downstaged to non-muscle-invasive disease; these numbers are comparable to those with NAC alone.

The recently published phase 2 PURE-01 trial (Neoadjuvant Pembrolizumab for Muscle-Invasive Urothelial Bladder Carcinoma) reported results for 50 of the 71 enrolled patients. The study included patients with cT2 (42%), cT3 (54%), and cT2-T3 N1(4%) MIUBC, who went on to receive 3 cycles of neoadjuvant pembrolizumab (Keytruda, Merck) regardless of cisplatin eligibility; 92% were cisplatin eligible. This trial showed a 42% pCR rate and a 54% rate of disease at a stage less than pT2.<sup>28</sup> According to biomarker analysis, pT0 was achieved in 54.3% of patients with a PD-L1 combined positive score of 10% or higher vs 13.3% of those with a PD-L1 combined positive score of less than 10%. Furthermore, a significant nonlinear association was seen between tumor mutation burden and pT0, with a cutoff

at 15 mutations per megabase ( $P=.022$ ).<sup>28</sup>

Another small, single-arm presurgical trial has reported on 12 patients with high-risk MIUBC who are ineligible for cisplatin-based chemotherapy; they received 1500 mg of durvalumab (Imfinzi, AstraZeneca) plus 75 mg of tremelimumab at weeks 1 and 5. Of the 6 patients who had undergone radical cystectomy at the time of data cut-off, 3 (50%) achieved a pCR, 1 (17%) did not respond, and 2 (33%) had their disease upstaged.<sup>29</sup>

Hoimes and colleagues presented a cisplatin-eligible cohort of 40 patients with T2-T4a N0 M0 bladder cancer; these patients received neoadjuvant treatment with 4 cycles of GC and 4 cycles of pembrolizumab (given on day 8 of a 21-day protocol). The pT0 rate was 40% (16 patients). Downstaging to non-muscle-invasive disease ( $\leq$ pT1) occurred in 61% of patients. The responses occurred in patients with PD-L1-negative (PD-L1<10%) and PD-L1-positive (PD-L1>10%) tumors.<sup>30</sup> Taken together, these data are encouraging, but long-term outcomes are needed before immunotherapy can be used alone or in combination with chemotherapy in the neoadjuvant setting in the clinic. On the basis of these results, phase 3 trials are being designed and initiated (eg, pembrolizumab plus GC vs GC alone).

### Neoadjuvant Therapy in Upper Tract Urothelial Carcinoma

UTUC constitutes 5% of all urothelial cancers.<sup>31</sup> Radical nephroureterectomy is the definitive treatment for

**Table 3.** Summary of Selected Clinical Trials of Adjuvant Chemotherapy for Bladder Cancer

Study First Author	No. of Pts	Stage, TNM	Chemotherapy	OS, Chemotherapy vs Observation
Skinner <sup>36</sup>	91	pT3-4 or N+	Cisplatin, doxorubicin, and cyclophosphamide	Median OS: 4.3 vs 2.4 y ( $P=.0062$ )
Lehmann <sup>38</sup>	49	pT3b-4a and/or pN1-2	MVAC or MVEC	10-y OS rate: 26.9% vs 17.4% ( $P=.069$ )
Freiha <sup>39</sup>	50	pT3b-4 N0 or N1	CMV	Median OS: 63 vs 36 mo ( $P=.32$ )
Studer <sup>40</sup>	77	Stratification: low-stage ( $\leq$ pT3a) vs high-stage (T3b-4a), pN0 vs N1-2	Cisplatin	5-y OS rate: 57% vs 54% ( $P=.65$ )
Paz-Ares <sup>41</sup>	142	pT3-4 and/or N+	PGC	5-y OS rate: 60% vs 31% ( $P<.0009$ )
Cognetti <sup>42</sup>	194	pT2G3, pT3-4, N0-2	GC	5-y OS rate: 43.4% vs 53.7% ( $P=.24$ )
Sternberg <sup>43</sup>	284	pT3-4 or pN1-3	GC or high-dose MVAC	5-y OS rate (immediate vs deferred treatment): 53.6% vs 47.7% ( $P=.13$ )

CMV, cisplatin, vinblastine, and methotrexate; GC, gemcitabine and cisplatin; mo, months; MVAC, methotrexate, vinblastine, doxorubicin, and cisplatin; MVEC, methotrexate, vinblastine, epirubicin, and cisplatin; No., number; OS, overall survival; PGC, paclitaxel, gemcitabine, and cisplatin; pts, patients; TNM, tumor node metastasis; y, year.

these patients.<sup>32</sup> Given the rarity of the disease, no level 1 evidence for neoadjuvant or adjuvant chemotherapy existed until recently. A meta-analysis of 31 trials with 8100 patients showed a significant improvement in disease-specific survival (DSS) in the NAC group relative to the control group (HR, 0.25; 95% CI, .06-0.61) and an improvement in DSS when NAC was compared with adjuvant chemotherapy (HR, 0.36; 95% CI, 0.08-0.90).<sup>33</sup>

In a retrospective study by Matin and colleagues, 107 patients with UTUC in a control group underwent surgery alone and 43 patients were treated with NAC before surgery. NAC was associated with a pCR rate of 14%.<sup>34</sup>

In the recent prospective phase 2 ECOG-ACRIN 8141 trial (Chemotherapy Before Surgery in Treating Patients With High Grade Upper Urinary Tract Cancer), 36 patients received 4 cycles of either DD MVAC (those with creatinine clearance [CrCl]  $>50$  mL/min;  $n=30$ ) or GC (those with CrCl of 30-50 mL/min;  $n=6$ ). The GC arm did not meet its accrual goal and was closed after 6 patients had been enrolled. The pCR rate in the DD MVAC arm was 14% (4/29), and disease was downstaged to pT1 or lower in 62% (18/29) of the patients. DD MVAC was felt to be safe and well tolerated.<sup>35</sup> Because of the encouraging rates of pCR and downstaging to pT1 or less following DD MVAC in this trial, NAC in UTUC will be studied further.

## Adjuvant Chemotherapy in Bladder Carcinoma

Several prospective trials were designed to determine the potential efficacy of adjuvant chemotherapy in patients with bladder cancer (Table 3). The first trial that showed a survival benefit with adjuvant chemotherapy was conducted by Skinner and colleagues. In this trial, 91 patients with pT3-4 or N+ bladder cancer received 4 cycles of adjuvant cisplatin, doxorubicin, and cyclophosphamide vs observation. Median OS was 4.3 years in the chemotherapy group vs 2.4 years in the observation group ( $P=.0062$ ).<sup>36</sup> Another prospective trial planned to enroll 83 patients with pT3b-4a and/or pN1-2. This trial was terminated after enrollment of 49 patients because of a significant prognostic advantage in PFS in favor of the chemotherapy group ( $P=.0005$ ). Patients received 3 cycles of adjuvant MVAC or MVEC (methotrexate, vinblastine, cisplatin, and epirubicin) vs no adjuvant therapy.<sup>37</sup> After 10 years of follow-up, adjuvant chemotherapy improved PFS ( $P=.002$ ), OS ( $P=.069$ ), and tumor-specific survival ( $P=.007$ ).<sup>38</sup> Freiha and colleagues enrolled 50 patients with pT3b-4 N0 or N1 urothelial bladder cancer, who received either 4 cycles of adjuvant cisplatin, methotrexate, and vinblastine (CMV) or observation. Median PFS was 37 months in the adjuvant chemotherapy arm vs 12 months in the observation arm ( $P=.01$ ). Median OS



was 63 months in the adjuvant arm vs 36 months in the observation arm, but the difference was not statistically significant ( $P=.32$ ), potentially owing to a small sample size and the fact that some patients in the observation arm were treated with CMV at relapse.<sup>39</sup> Another trial randomly assigned 77 patients after radical cystectomy to 3 courses of high-dose cisplatin monotherapy (90 mg/m<sup>2</sup> at monthly intervals) vs observation. No statistically significant difference in OS was observed (log-rank  $P=.65$ ).<sup>40</sup>

The Spanish Oncology Genitourinary Group (SOGUG) compared 4 cycles of adjuvant paclitaxel, gemcitabine, and cisplatin (PGC) with observation in patients who had pT3-4 and/or pN+ bladder cancer. This trial closed early, after enrollment of 142 patients, owing to poor recruitment. However, OS ( $P<.0009$ ), disease-free survival (DFS;  $P<.0001$ ), time to progression (TTP;  $P<.0001$ ), and DSS ( $P<.0002$ ) were superior in the chemotherapy arm.<sup>41</sup>

In 2 randomized phase 3 trials, patients with advanced bladder cancer were assigned to either adjuvant chemotherapy or chemotherapy at relapse.<sup>42,43</sup> Cognetti and colleagues enrolled 194 patients with pT2G3, pT3-4, N0-2 bladder cancer. After surgery, patients were randomly allocated to receive 2 different schedules of adjuvant GC or observation and treatment at relapse. Because of poor accrual, this trial closed early. No difference was found between OS ( $P=.24$ ) and DFS ( $P=.70$ ) in the 2 arms. In addition, only 62% of the patients completed all 4 treatment cycles.<sup>42</sup>

EORTC 30994 (Comparison of Immediate and Delayed Adjuvant Chemotherapy in Treating Patients Who Have Undergone a Radical Cystectomy for Stage III or Stage IV Transitional Cell Carcinoma of the Bladder Urothelium) was a phase 3 trial that enrolled 284 (of the planned 660) patients with pT3-4 or pN1-3 M0 disease after radical cystectomy. Patients were randomly assigned to either immediate adjuvant chemotherapy (4 cycles of GC or DD MVAC) or deferred chemotherapy (6 cycles of GC or DD MVAC) at the time of relapse. This trial showed a significant increase in median PFS in the immediate- vs the deferred-treatment arm (3.11 vs 0.99 years; HR, 0.54; 95% CI, 0.40-0.73;  $P<.0001$ ), but no significant improvement in OS. The 5-year OS rate was 53.6% in the immediate arm vs 47.7% in the deferred arm ( $P=.13$ ).<sup>43</sup> This trial did not meet its original target accrual.

A retrospective National Cancer Data Base analysis by Galsky and colleagues included 5653 patients with pT3-4 and/or N+ bladder cancer, of whom 23% received adjuvant polychemotherapy. When stratified analysis adjusted for propensity score was used, adjuvant chemotherapy was associated with an OS benefit (HR, 0.70; 95% CI, 0.64-0.76). The 5-year OS rate was 37% in the

adjuvant chemotherapy group vs 29.1% in the observation group ( $P<.001$ ).<sup>44</sup>

These findings collectively indicate that adjuvant cisplatin-based chemotherapy can be offered as an option to all eligible patients with higher than pT2 urothelial carcinoma after surgery if no NAC has been administered.

### Adjuvant Chemotherapy in Upper Tract Urothelial Carcinoma

Although several adjuvant trials in MIUBC failed to complete accrual, a retrospective study and now a completed prospective study (POUT, A Phase III Randomised Trial of Peri-Operative Chemotherapy Versus Surveillance in Upper Tract Urothelial Cancer) support the use of adjuvant chemotherapy in UTUC. According to one large meta-analysis, adjuvant chemotherapy vs control treatment in UTUC improved OS, DSS, and recurrence-free survival by 32%, 29%, and 51%, respectively.<sup>33</sup> In a separate meta-analysis of 1 prospective and 9 retrospective trials, Leow and colleagues demonstrated benefit in OS and DFS with cisplatin-based adjuvant chemotherapy. The benefit was not seen in non-cisplatin-based regimens.<sup>45</sup>

However, the strongest evidence for adjuvant chemotherapy in UTUC comes from POUT, which included 261 patients who underwent radical nephroureterectomy for pT2-4 N0 M0 or pT-any N1-3 M0 disease and then were randomized to receive platinum-based chemotherapy based on their glomerular filtration rate (GFR) or surveillance.<sup>46</sup> The chemotherapy regimen was gemcitabine at 1000 mg/m<sup>2</sup> on days 1 and 8, with cisplatin at 70 mg/m<sup>2</sup> on day 1 (GFR,  $\geq 50$  mL/min) or carboplatin at an area under the curve (AUC) of 4.5 or 5 (GFR, 30-49 mL/min). Adjuvant chemotherapy was associated with a statistically significant benefit in DFS (HR, 0.49; 95% CI, 0.31-0.76;  $P=.001$ ), which was the primary endpoint, and metastasis-free survival (HR, 0.49; 95% CI, 0.30-0.78;  $P=.002$ ). A trend toward improved OS was also noted, with numerical improvement seen (HR, 0.55). Follow-up for OS is ongoing. On the basis of these results, adjuvant platinum-based chemotherapy should be considered a new standard of care in patients with UTUC, particularly if they remain platinum-eligible and did not receive NAC.

### Neoadjuvant vs Adjuvant Chemotherapy in Bladder Carcinoma

Although no prospective trials have directly compared NAC with adjuvant chemotherapy in urothelial cancer, a few retrospective trials have attempted to answer the question of which approach is better. A recent retrospective cohort study showed that only 20.8% of patients received

NAC, and 39.8% received perioperative chemotherapy.<sup>47</sup> The rates of preoperative chemotherapy have increased steadily (from 10.1% in 2006 to 20.8% in 2010), whereas the use of adjuvant chemotherapy has remained constant.<sup>47</sup>

Two of the reasons for the underuse of NAC are the perceived modest benefit and concerns about overtreatment; many believe that a 5% gain in OS is not sufficient to recommend NAC for all patients.<sup>48</sup> However, in a retrospective review of 212 patients with cT2 N0 M0 urothelial bladder cancer, the tumors of 73.2% were upstaged to pT3/T4 or N+ at surgery without NAC. Only 37.9% of these patients received adjuvant chemotherapy.<sup>49</sup> Also, a retrospective review of 878 patients showed that NAC did not increase perioperative complications or surgical morbidity.<sup>50</sup> Finally, the use of adjuvant cisplatin-based combination regimens may be limited owing to prolonged postoperative recovery and a high prevalence of renal impairment in patients with high-risk bladder cancer.<sup>51</sup>

To underscore one extreme, Martin and colleagues analyzed 235 patients from a prospective database and found that only 2.2% of patients had received NAC before radical cystectomy. According to a questionnaire that was used in this analysis, 45% of urologists would not administer NAC.<sup>52</sup> However, in a retrospective review of 261 patients who underwent radical cystectomy between 2008 and 2012, Krabbe and colleagues showed an increase in the rate of overall utilization of NAC from 22% to 41%.<sup>53</sup>

Although no prospective direct comparison of neoadjuvant vs adjuvant chemotherapy in MIUBC has been undertaken, a prospective phase 3 trial compared perioperative with adjuvant chemotherapy. In the trial, 140 patients with cT3b-4 N0 disease or cT1-3a N0 disease with lymphovascular invasion received 2 courses of neoadjuvant MVAC followed by surgery plus 3 cycles of adjuvant MVAC vs 5 cycles of adjuvant MVAC. A difference between survival in the 2 groups was not found.<sup>54</sup>

When the findings are taken together, the consensus is to recommend NAC for patients with MIUBC.<sup>11</sup> Adjuvant chemotherapy is usually given after radical cystectomy for patients with locally advanced disease (>pT2) who did not receive NAC. Finally, 3 large prospective phase 3 trials are evaluating atezolizumab (IMvigor010; NCT02450331), pembrolizumab (AMBASSADOR; NCT03244384), and nivolumab (CheckMate 274; NCT02632409) as adjuvant treatment in patients with high-risk MIUBC after surgery.

## Conclusion

Neoadjuvant cisplatin-based chemotherapy is supported by level 1 evidence and is a standard of care for eligible

patients with MIUBC. For those who did not receive NAC, adjuvant cisplatin-based chemotherapy should be considered in stage pT3 or higher disease. In UTUC, adjuvant chemotherapy provides an OS benefit, but NAC should be used if possible. Current clinical trials are focused on immunotherapy alone or in combination with chemotherapy as neoadjuvant treatment, as well as on treatment allocation based on biomarkers to allow bladder preservation.

## Disclosures

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