CLINICAL INVESTIGATION

Neoadjuvant chemotherapy in bladder cancer

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The use of neoadjuvant chemotherapy is an important element in the management of advanced bladder cancer. While definitive surgical management of locally advanced disease remains the gold standard of treatment, evidence over the years has repeatedly and consistently demonstrated the survival benefits of presurgical systemic chemotherapy. Incorporation of neoadjuvant chemotherapy into the treatment of urothelial carcinoma is based upon the following assumptions: administering chemotherapy prior to surgery may render tumors resectable through down-staging; chemotherapy can eradicate micrometastatic disease already present at the time of diagnosis, thereby reducing the risk of local and distant recurrence and improving overall survival; and, the preoperative setting represents a window of opportunity for the safe delivery of the recommended doses of chemotherapy. In this review, the authors examine the evidence for chemotherapy in the neoadjuvant setting and discuss ongoing advances in the field.

Keywords: bladder cancer • neoadjuvant chemotherapy • urothelial carcinoma

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Bladder cancer is the ninth most common malignancy worldwide with an annual incidence of 382,660 cases and 150,282 deaths, according to 2008 estimates [1]. The most curable patients (~75%) are those diagnosed with non-muscle invasive disease (<pT2); they are typically managed with transurethral resection with or without intravesical therapy (Bacillus Calmette-Guerin or chemotherapy [e.g., mitomycin]) when necessary. Surveillance with cystoscopic monitoring is required at regular intervals because of the high rate of recurrence and subsequent progression to more advanced disease, particularly in those with high grade urothelial carcinoma (UC). The least curable subset is the 5% of patients who present with metastatic disease and are managed with systemic chemotherapy. Those patients with an intermediate prognosis, and the focus of this review, are the approximately 20% who present with muscle-invasive or locally advanced disease. For these patients, definitive management includes either surgery comprised of radical cystectomy (RC) and bilateral pelvic lymph node dissection or alternatively, multimodality chemoradiotherapy with the intent of bladder preservation (Figure 1).

In the group of patients with muscle-invasive cancer managed with primary cystectomy and lymph node dissection, disease stage at presentation has a significant impact on individual patient outcomes and long-term survival. In a retrospective series of 1054 patients, the 5- and 10-year recurrence-free and overall survival (OS) in organ-confined, lymph-node-negative disease was 85 and 82%, and 78 and 56%, respectively. Patients with lymph-node-positive disease had significantly worse survival outcomes with 5- and 10-year recurrence-free and OS of 35 and 35%, and 31 and 23%, respectively [2]. Due to the poor prognosis of lymph-node-positive or distant metastatic disease, with an estimated median OS between 14–15 months and 5-year OS of 15% [3], efforts have focused upon the early eradication of micrometastatic spread with perioperative chemotherapy. The use of neoadjuvant chemotherapy

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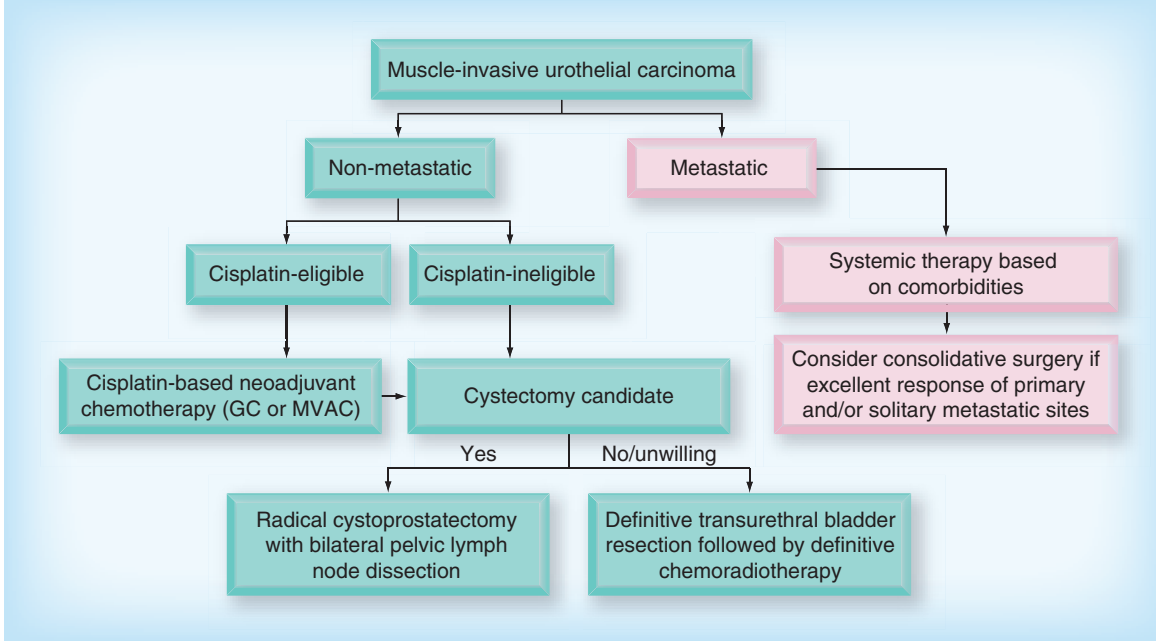

Figure 1. Muscle-invasive bladder cancer treatment algorithm.
GC: Gemcitabine and cisplatin; MVAC: Methotrexate, vinblastine, doxorubicin and cisplatin.

(NAC) in muscle-invasive bladder cancer (MIBC) is an attractive treatment option given the general chemosensitivity of UC, the lack of NAC-associated surgical complications [2], and the difficulty of administering treatment in the adjuvant setting owing to surgical morbidity and postoperative complications [4].

The aim of this review is to assess the evidence and rationale for the use of NAC in the management of UC. We will assess how clinical studies and meta-analyses have answered the following important questions:

- What is the significance of achieving a tumor response to NAC?
- What is the historical context for NAC?
- Which NAC drug combinations are preferred in the management of muscle invasive UC?
- What dosing schedule options are available?
- What is the role of NAC in upper tract disease?
- What is the role of NAC in cisplatin-ineligible patients?
- What novel agents are being evaluated in the neoadjuvant setting?

What is the significance of achieving a tumor response to NAC?

The use of NAC prior to definitive surgery is a widely used treatment modality in a variety of solid tumor subtypes (bladder [5], breast [6], rectal [7], lung [8] and so forth), each with the similar goal of improving patient outcomes via tumor down-staging, elimination of micrometastatic disease, and the improved ability to administer effective doses of chemotherapeutic agents compared with the postoperative setting. In bladder cancer, achieving any degree of pathologic response within the primary tumor translates into improved survival rates. Splinter and colleagues demonstrated this benefit in a retrospective analysis showing that, in patients who had received neoadjuvant methotrexate, vinblastine, doxorubicin and cisplatin (MVAC) or cisplatin plus methotrexate prior to RC, 5-year survival for those achieving a major pathological response (<pT2) versus no pathological response (≥pT2 disease) was 75 versus 20%, respectively ($p < 0.0001$) [9]. In another retrospective study of patients receiving MVAC preoperatively, achieving ≤pT3a (organ-confined) response versus ≥pT3b (non-organ-confined) was associated with an improved 5-year survival advantage (61 vs 35%, respectively). This benefit was present irrespective of whether a pathologic complete response (pCR) was achieved in the organ-confined specimens [10]. Retrospective analyses consistently show that a lower disease stage at the time of surgical resection is associated with an improved survival, irrespective of whether the patients received NAC or a diagnostic transurethral resection [11,12]. For example, in one series, 5-year OS was 89% in patients with pCR, whereas it was 60% in pT2 and 47% in >pT2 disease [13]. In each example, the

relative degree of disease invasion through the bladder wall defined a different risk population and these results served as a surrogate for predicting OS. Partly based on these early retrospective reviews, the degree of pathologic response serves as a prognostic marker for survival as well as the efficacy of NAC. Throughout this review, we will describe a number of clinical trials of NAC comprising differing numbers of chemotherapeutic agents in varying combinations and dosing schedules. Although distinct in design, all of these trials repeatedly underscore the correlation between pathologic response and long-term survival.

What is the historical context for NAC?

The seminal trials of NAC utilized an older version of the American Joint Committee on Cancer staging criteria in which pT3 disease included both deep muscularis and perivesical invasion. Please refer to Table 1 for all trials described in this section.

Nordic cystectomy trials

One of the earliest trials evaluating NAC was the Nordic Cystectomy Trial I [14]. In this study, 311 eligible patients with locally advanced stage T1 grade 3 or stage T2 to T4a NXMO UC were randomized to NAC with cisplatin (70 mg/m^2) and doxorubicin (30 mg/m^2) for a total of two cycles at 3-week intervals followed by radiotherapy (20 Gy) and RC versus radiotherapy and RC alone. At 5 years of follow up, there was no significant difference between the NAC-treated and control arms in terms of OS (59 vs 51%; p = 0.1) or cancer-specific survival (64 vs 54%; p = 0.07), respectively. A subset analysis did reveal a 15% absolute survival benefit in patients with T3 to T4a disease receiving NAC (p = 0.03). The follow up Nordic Cystectomy Trial II restricted the treatment population to patients with MIBC or higher stage, eliminated preoperative radiotherapy in both arms, increased the number of cycles of neoadjuvant therapy, and modified the drugs administered [15]. In this study, 309 patients with T2 to T4a NXM0 UC were randomized to NAC with cisplatin (100 mg/m^2) and methotrexate (250 mg/m^2) for three cycles given at 3 week intervals followed by RC versus RC alone. At 5 years of follow up, even in a population of higher risk, higher stage patients treated with an increased duration of chemotherapy (three vs two cycles), OS was not significantly different between the two arms (53% with chemotherapy plus RC vs 46% with RC alone; p = 0.2). Ultimately, neither Nordic trial was sufficiently powered to detect small improvements in OS. A subsequent intention-to-treat analysis combining data from both trials was performed which revealed a statistically significantly improved 5-year OS of 56 versus 48% (hazard ratio [HR]: 0.80; 95% CI: 0.64–0.99; p = 0.049) [16], which translated into an 8% absolute reduction in mortality. Furthermore, a more recent analysis of these combined data demonstrated that, in those patients who achieved a pCR within the resected cystectomy specimen, an absolute risk reduction (ARR) in death of 31.1% in favor of NAC plus RC was observed. This survival benefit observed with NAC was evidenced in patients with non-muscle invasive residual disease (pTa, pTcis, pT1; ARR: 17.9%; p = 0.018) and organ-confined residual disease (≤pT2; ARR: 12.9%; p = 0.005) when compared with patients with residual non-organ confined disease (≥pT3) [17]. These trials provided initial evidence for the potential role of cisplatin-based combination chemotherapy in the neoadjuvant setting and established the response and survival paradigm for future NAC trials.

Cisplatin, methotrexate & vinblastine

Given the trend towards a survival benefit with neoadjuvant cisplatin doublets, the impact of incorporating other

Table 1. Historical neoadjuvant trials.

Clinical trial	Patients (n)	Neoadjuvant regimen (cycles)	Primary treatment	Median OS with/without neoadjuvant therapy (%)	Survival benefit	Ref.
Nordic Cystectomy I	325	CA (2)	RT+RC	59/51 at 5 years (p = 0.1)	No	[14]
Nordic Cystectomy II	317	CM (3)	RC	53/46 at 5 years (p = 0.2)	No	[15]
Nordic Cystectomy Combined Analysis	620	CA or CM	RT+RC or RC	56/48 at 5 years (p = 0.49)	Yes	[16]
International Collaboration of Trialists	976	CMV (3)	RC	36/30 at 8 years (p = 0.003)	Yes	[19]
SWOG/US Intergroup	317	MVAC (3)	RC	57/43 at 5 years (p = 0.06)†	No	[23]
ABC meta-analysis collaboration	3005	Various	Various	50/45 at 5 years (p = 0.003)	Yes	[5]

†Based on two-tailed statistical analysis as per publishing journal but trial designed as one-tailed, which did reach statistical significance.

A: Adriamycin (doxorubicin); C: Cisplatin; M: Methotrexate; OS: Overall survival; RC: Radical cystectomy; RT: Radiotherapy; V: Vinblastine.

synergistic agents was explored. In the largest trial to date evaluating the role of NAC in MIBC, a multinational, Phase III study (BA06 30894) comparing three cycles of neoadjuvant cisplatin (100 mg/m^2), methotrexate (30 mg/m^2) and vinblastine (4 mg/m^2; CMV) administered every 3 weeks to non-neoadjuvant therapy was performed through the International Collaboration of Trialists. A total of 976 patients with stage T2-T4a N0/X M0 bladder cancer and a glomerular filtration rate > 50 ml/min were randomized to NAC or no therapy prior to predetermined definitive local therapy (RC, radiotherapy or radiotherapy plus RC) defined prior to randomization [18]. The primary end point of the study was to detect a 10% improvement in 3-year survival with the addition of NAC. In the final analysis, 43% of patients received definitive radiotherapy, 49% RC alone and 8% received a combination of the two. At 3 years of follow up, a nonsignificant 5.5% absolute difference in survival was observed favoring NAC (55.5% with NAC vs 50.0% with no chemotherapy; p = 0.075). However, in a subsequent analysis at a longer median follow up of 8 years, a statistically significant 16% reduction in the risk of death (HR: 0.84; 95% CI: 0.72–0.99; p = 0.037) was demonstrated, corresponding to a 10-year survival improvement from 30 to 36% [19]. A subset analysis revealed that patients whose primary tumors were managed with cystectomy fared the best, with a 26% relative reduction in the risk of death (HR: 0.74; p = 0.022) for those receiving NAC compared with surgery alone. Of the patients who underwent cystectomy, the pCR rate with NAC versus without NAC was 32.5 versus 12.3%, respectively. Further subset analyses suggested that neoadjuvant CMV may have had a greater effect in patients with better renal function, large tumor size and poorly differentiated tumors. There was also no evidence that chemotherapy adversely impacted local definitive therapy, regardless of type. Furthermore, the toxic death rate from chemotherapy was only 1%, underscoring the overall tolerability of the CMV regimen. This NAC survival benefit is substantial in light of the potentially confounding issues of heterogeneous surgical techniques used for RC, the high percentage of patients with possible stage IV disease (NX stage: 33%) and the relative under treatment of patients (20% of NAC arm did not receive three cycles) that could have adversely affected the observed benefit. Although this regimen is not currently used in standard clinical practice, it does provide some of the clearest evidence for the benefit of neoadjuvant cisplatin-based therapy in MIBC.

Which NAC drug combinations are preferred in the management of muscle invasive UC?

■ Southwest Oncology Group/Intergroup study

A Southwest Oncology Group (SWOG) trial explored the role of four drugs in the neoadjuvant setting. The MVAC regimen was initially studied at Memorial Sloan-Kettering Cancer Center (MSKCC) in the 1980s with significant activity observed in advanced disease. Initial studies in metastatic UC noted a 72 ± 8% response rate with clinical complete responses (cCR) in 36 ± 9% of patients [20]. MVAC activity in the advanced setting was subsequently confirmed in multiple trials, albeit with less impressive response rates, establishing the MVAC regimen as the *de facto* standard of care for metastatic UC [21]. An early retrospective analysis of the MSKCC experience with neoadjuvant MVAC demonstrated promising activity. In this review, 111 with T2–3N0M0 MIBC received neoadjuvant MVAC, and 60 patients (54%) achieved a cCR as evaluated by transurethral resection of bladder tumor (TURBT). Of these 60 patients, 43 underwent bladder-sparing surgery and 74% were still alive after an average follow up of 10 years with 58% having an intact functioning bladder [22]. These findings underscore the efficacy of NAC in rendering pCRs and resultant long-term survival.

The SWOG 8710/INT-0080 Phase III trial was initiated to evaluate prospectively the potential benefit of neoadjuvant MVAC followed by RC. In this US-based trial, 317 patients with T2-T4aN0M0 bladder cancer who were eligible for RC and cisplatin-based chemotherapy were randomized to NAC with methotrexate (30 mg/m^2), vinblastine (3 mg/m^2), doxorubicin (30 mg/m^2) and cisplatin (70 mg/m^2) for three 28-day cycles followed by RC versus RC alone [23]. Based on an intention-to-treat analysis of 307 eligible patients, median survival with combination therapy was 77 versus 46 months with surgery alone (p = 0.06 by two-sided stratified log-rank test). Although the trial did not reach statistical significance based on the two-sided analysis as dictated by the publishing journal, it is still considered to be a positive trial as the initial cutoff for statistical significance was a one-sided p < 0.05. Furthermore, NAC resulted in an increased rate of pCR (38 vs 15%) compared with surgery alone. pCR is considered a critical benchmark because patients who achieved pCR had a 5-year OS of 85% in contrast to patients with residual UC in the bladder, whose 5-year OS was approximately 50%. NAC also reduced the positive surgical margin rate, from 14% seen in patients treated with cystectomy alone to 7% in patients treated with neoadjuvant MVAC. The reduced positive margin rate is an extremely important finding given the close relationship between positive margins and subsequent relapse and death. In a subsequent retrospective analysis, patients with residual UC in the bladder (pTa, pT1, pTcis, pT2+), positive lymph nodes or suboptimal lymph node dissection (fewer than ten lymph nodes removed), had

worse survival outcomes than the comparator group of patients with pCR, negative lymph nodes and ten or more lymph nodes removed [24]. The SWOG study supports the use of MVAC in the neoadjuvant setting in appropriately selected patients. The results of this study and the International Collaboration of Trialists study provide the highest level of evidence for the use of NAC in MIBC.

Gemcitabine & cisplatin

While the rationale for using MVAC in both the metastatic and neoadjuvant settings is based on improved response rates, progression-free survival (PFS) and OS in both disease states [20,23], the toxicities associated with this regimen are significant. When given preoperatively, patients who received MVAC experienced granulocytopenia (grade 4: 33%), stomatitis (grade 3: 10%) and a combined gastrointestinal toxicity of nausea, vomiting, diarrhea or constipation (grade 3: 10%) [23]. The gemcitabine and cisplatin (GC) regimen has largely replaced MVAC in the metastatic disease setting based on a Phase III trial. This use of GC stems from the desire to avoid the toxicity of the MVAC regimen while maintaining its efficacy. As a single agent for the treatment of cisplatin-refractory or cisplatin-ineligible metastatic disease, gemcitabine (1000 mg/m^2) on a weekly schedule has an overall-response rate of 22.5% (95% CI: 8–37%) with a median OS of 5 months [25]. The efficacy of the combination of GC in metastatic disease was established by von der Maase and colleagues in a Phase III trial comparing MVAC and GC. In initial results reported in 2000 and updated in 2005, similar PFS (7.7 vs 8.3 months) and OS (14.0 vs 15.2 months; HR: 1.09; 95% CI: 0.88–1.34; p = 0.66) were noted between GC and MVAC, respectively [3]. The MVAC arm, however, was associated with higher rates of neutropenic fever (14 vs 2%), neutropenic sepsis (12 vs 1%), grades 3/4 mucositis (22 vs 1%) and alopecia (55 vs 11%) when compared with GC [26]. Although GC was associated with an increased incidence of grades 3/4 anemia (27 vs 18%) and grades 3/4 thrombocytopenia (57 vs 21%) compared with MVAC, the regimen was seen as a significant improvement in terms of toxicity.

Based on this comparable effectiveness and improved tolerability in the advanced setting, GC was also evaluated in the neoadjuvant setting. The first retrospective analysis was from MSKCC comparing 42 patients who received GC and 54 patients who received MVAC. The proportion of patients who achieved a pCR (26 vs 28%) and <pT2 response (36 vs 35%) was comparable between GC and MVAC, respectively [27]. Subsequent retrospective studies from other centers confirmed this initial finding, observing similar pCR rates between GC and MVAC without either regimen predicting for superior cancer-specific survival [28,29]. Another retrospective study of neoadjuvant GC at q3week or q4week dosing intervals noted a pCR rate of 38% and <pT2 rate of 62% in patients who received NAC followed by definitive surgery [30]. When assessing patients who had pCR, cCR or down-staging to non-MIBC, all were alive at a median of 16 months post intervention. Finally, a small prospective Phase II trial of neoadjuvant GC in 22 patients confirmed the pCR rate of 26.7% with a median PFS of 26 months and a median OS of 36 months [31]. Implicit in the support for the use of neoadjuvant GC is the acceptance that comparable rates of pCR between GC and MVAC are an appropriate surrogate of long-term treatment effectiveness and survival. While this evidence for the use of neoadjuvant GC is based upon an amalgamation of retrospective studies, a small prospective trial, and extrapolation from efficacy in the advanced setting, GC is frequently a first-line NAC choice based on physician and patient preference.

Meta-analysis

The survival benefit associated with NAC was best encapsulated in the Advanced Bladder Cancer Meta-analysis Collaboration, which analyzed 3005 patients from 11 trials and incorporated 98% of all patients from known randomized clinical trials to date to define the impact of NAC in the treatment of patients with MIBC [5]. These pooled results demonstrated a 14% reduction in risk of death, translating to a 5% absolute survival benefit at 5 years (HR = 0.86; 95% CI: 0.77–0.95; p = 0.003) for patients treated with neoadjuvant, cisplatin-based, chemotherapy. This absolute survival benefit is comparable to that seen in both breast and colon cancer patients, albeit in the adjuvant setting in these cancers. For example, the Early Breast Cancer Trialists' Collaborative Group, a meta-analysis of 17,723 early stage breast cancer patients receiving adjuvant polychemotherapy, showed an estimated 7% absolute survival benefit at 10 years with adjuvant therapy [32]. Similarly, a pooled analysis of colorectal cancer patients receiving adjuvant 5-fluorouracil demonstrated an absolute survival benefit of 7% at 5 years with the use of postoperative chemotherapy [33]. The Advanced Bladder Cancer meta-analysis firmly established the benefit of NAC and its role in the management of locally advanced MIBC.

What dosing schedule options are available?

Alternative dosing schedules of cisplatin-based NAC have been explored as a means of further optimizing disease response and survival outcomes. A common strategy has been to intensify the dosing frequency of treatment from every 3 or 4 weeks to every 2 week

cycles. As Citron and colleagues demonstrated in CALGB 9741, using an every 2 week dosing schedule with G-CSF support in the adjuvant treatment of breast cancer improved OS with comparable toxicity profiles [34]. Building on these findings, a number of studies have evaluated the efficacy and safety of this dose-dense (DD) schedule in both the advanced and neoadjuvant setting in UC. In the advanced setting, Sternberg and colleagues reported an improved cCR (25 vs 11%; p = 0.006) and PFS (9.5 vs 8.1 months; HR = 0.73; 95% CI: 0.56–0.95; p = 0.017) with similar safety in a 2 versus 4 week MVAC schedule, respectively [21]. Similarly, the Hellenic Oncology Group compared DD-MVAC and DD-GC in the advanced/metastatic setting and observed a similar PFS (8.5 vs 7.8 months; p = 0.36) and OS (19 vs 18 months; p = 0.098), respectively, between the regimens and improved tolerability and less toxicity with DD-GC [35].

Acknowledging the survival benefit associated with neoadjuvant cisplatin-based therapy and the recurring observation that pCR patients have improved survival, the use of DD regimens in the neoadjuvant setting is an attractive avenue to potentially improve pCR rates. Elmongy and colleagues reported a 50% pCR rate in a small feasibility study of 12 patients who received DD-MVAC prior to RC [36]. A retrospective analysis of 80 patients with T2–4a, N0–2, M0 disease treated with three or four cycles of DD-MVAC followed by RC or definitive radiotherapy showed that, in the 60 patients who underwent radical cystectomy, 24 patients (40%) were free of disease in the resected specimen. Furthermore, 31/60 patients (52%) had <pT2 disease and the 2-year disease-free survival and OS were 65 and 77%, respectively [37]. Finally, two prospective Phase II trials of DD-MVAC noted pCR rates in 39.4 and 26% of patients, respectively, with additional patients exhibiting noninvasive or clinically downstaged disease [38,39]. While there is a growing body of literature regarding neoadjuvant DD-MVAC at the time of this publication, there are no peer-reviewed publications examining DD modification of GC in the neoadjuvant setting. Based on the equivalence of both DD regimens in the advanced setting [3,35], the next logical step is the formal exploration of a DD-GC regimen in the neoadjuvant setting. Phase II trials are currently underway to examine the impact of neoadjuvant DD-GC on pCR proportions as a primary end point along with safety and patient tolerance. These studies will hopefully provide further clarification for the role of a DD strategy in MIBC.

See Table 2 for ongoing and completed clinical trials of alternative dosing schedules in the neoadjuvant setting.

What is the role of NAC in upper tract disease?

Upper tract UC (UTUC), defined as disease involving the renal pelvis and/or ureters, accounts for approximately 5% of all urothelial cancers, and primary disease management involves nephroureterectomy with bladder cuff removal [40]. However, given the high rates of disease recurrence, metastatic spread and the risk of understaging at the time of diagnosis, the use of NAC is increasingly being evaluated as a treatment option in upper tract disease. The theoretical benefits for a neoadjuvant strategy are based upon the same rationale for using NAC in the treatment of primary bladder tumors, including eradication of micrometastatic disease, the ability to administer adequate doses of chemotherapy in the setting of intact renal function [41,42], and the prognostic implications of tumor response and pathologic down staging [43]. In the retrospective International Upper Tract Urothelial Carcinoma Collaboration, 41/1363 (3%) patients with upper tract disease received NAC (regimens not reported) with 5/41 (12%) achieving a pCR in the resected specimens [44]. Similarly, two separate single institution, retrospective studies noted pCR responses in 6/43 (14%) and 2/15 (13%) in patients who received neoadjuvant chemotherapy [45,46]. Finally, another separate single-institution retrospective review from MD Anderson Cancer Center noted that patients with UTUC had improved 3-year disease-specific survivals (90 vs 64%) and pCR rates (19 vs 0%) when receiving neoadjuvant GC versus surgery alone [47]. While these retrospective analyses illustrate the potential benefit

Table 2. Dose-dense chemotherapy trials.

Regimen	Institution (location)	Patients (n)	Preliminary results	Ref
DD-MVAC	Fox Chase (PA, USA)	44	pCR 39% < pT2 48%, postoperative complications concerning	[38]
DD-MVAC	Dana-Farber (MA, USA)	39	pCR 26%, cN1 → pN0 82%	[39]
DD-GC	MSKCC (NY, USA)	N/A	Pathologic response rate (<pT2; results pending)	
DD-GC	Fox Chase	N/A	pCR (results pending)	
DD-MVAC	Fox Chase	N/A	pCR (results pending)	

A: Adriamycin (Doxorubicin); C: Cisplatin; DD: Dose-dense; G: Gemcitabine; M: Methotrexate; MSKCC: Memorial Sloan-Kettering Cancer Center; pCR: Pathologic complete response; V: Vinblastine.

of a neoadjuvant approach, prospective evidence for this treatment strategy is wanting. At the time of this publication, two ongoing Phase II trials are enrolling patients with high grade UTUC to receive neoadjuvant GC on an every 3 week schedule for four cycles prior to nephroureterectomy. The primary end point of one study is pathologic response rate (<pT2) and 2-year recurrence free survival in the other. Both of these studies will hopefully provide prospective data regarding the efficacy of NAC in upper tract disease.

What is the role of neoadjuvant chemotherapy in cisplatin-ineligible patients?

In the treatment of advanced/unresectable or metastatic bladder cancer, the standard of care remains the use of cisplatin-based regimens with either GC or MVAC serving as first-line options. However, up to 50% of patients are ineligible for cisplatin-based therapies due to a number of medical co-morbidities [48]. One consensus review proposed that patients with impaired renal function (CrCl <60 ml/min), poor performance status (Eastern Cooperative Oncology Group of 2 or Karnofsky performance status of 60–70% or less), Common Terminology Criteria for Adverse Events version 4 (CTCAEv4) grade ≥ 2 hearing loss by audiometry, CTCAEv4 grade ≥ 2 peripheral neuropathy or New York Health Association Class III heart failure [49] should be considered ineligible for cisplatin therapy except in rare circumstances. In the advanced setting, carboplatin is most frequently substituted for cisplatin with reduced, although continued efficacy [50]. Dogliotti and colleagues demonstrated this relative efficacy when comparing GC and gemcitabine-carboplatin (GCa) in the advanced setting. In this Phase II trial, median OS and median PFS between GC and GCa was 12.8 versus 9.8 months and 8.3 versus 7.7 months, respectively [50].

Given the persistent benefit of a platinum-based regimen in advanced UC, multiple trials have tested the efficacy of carboplatin-based regimens in the neoadjuvant setting. One small Phase II trial evaluated neoadjuvant paclitaxel, carboplatin and gemcitabine (PCaG) in patients with CrCl > 40 ml/min and adequate bone marrow and hepatic function. Patients were enrolled onto two arms defined by stage (T2–3N0M0 [arm 1] or T2–4N1–3M0 [arm 2]) with primary end points of pCR (arm 1) and resectability (arm 2) [51]. In the 22 evaluable patients in arm 1, seven (32%) had a pCR (22% in the intention to treat population). Although outside the scope of true NAC since patients with stage IV disease were included, patients in arm 2 receiving six cycles of PCaG had a resection rate of 67% (54% within the intention to treat population) with a pCR in five patients (16%). The toxicity associated with this regimen was considerable, with seven deaths (five during chemotherapy and two after cystectomy) related to treatment. A similar SWOG 0219 Phase II trial evaluated the efficacy of three cycles of PCaG followed by continued observation or RC. Of the 74 patients who were evaluable after neoadjuvant chemotherapy, 34 patients (46%) were deemed clinically free of disease on follow-up TURBT. Of these patients, ten underwent RC. In this subset, four patients had a pCR while the remaining six patients had residual pT2–4 UC [52]. These results not only indicate that post-NAC TURBT does not accurately assess true pathologic response (60% of patients exhibited residual disease at cystectomy), but that this response was also modest based on the entire trial population. Toxicity was also significant, with frequent myelosuppression and one death from neutropenic infection. PCaG seems to have limited activity and high toxicity in the neoadjuvant setting and consequently cannot be considered an appropriate option in patients ineligible for cisplatin-based therapy.

A separate Phase II trial in cisplatin-eligible patients evaluated the efficacy of methotrexate, carboplatin and vinblastine in the neoadjuvant setting and therefore serves as a potential reference for a similar regimen in cisplatin-ineligible patients [53]. In this trial, patients with T2–4N0M0 bladder cancer received the three-drug regimen on a 28-day schedule for four cycles with primary outcome of pCR. Of the 47 patients treated, pathological response was seen in 40% of patients with 12 patients (26.5%) achieving a pCR with a disease-specific survival of 42% at 2 years. Finally, the efficacy of GCa with nab-paclitaxel, the albumin-bound paclitaxel currently approved in non-small-cell lung cancer and breast cancer, has also been tested. Nab-paclitaxel is thought to have increased activity and decreased toxicity compared with standard paclitaxel preparations [54]. In total, 27 cisplatin-ineligible patients with T2–4N1–3M0 (stage IV) bladder cancer received three cycles prior to RC. The primary end point was pCR. Although complicated by high rates of neutropenia (all patients), only 7% (2/27) had febrile neutropenia. In terms of response rates, six out of 22 patients (27%) had a pCR, five out of 22 patients (23%) had residual carcinoma *in situ* and one patient harbored pT1 disease. In total, over half of the evaluable patients had no muscle-invasive disease after neoadjuvant chemotherapy. Barring any robust Phase III trial, it is difficult to recommend a carboplatin-based regimen in patients who are cisplatin-eligible or ineligible in the neoadjuvant setting. We therefore support the consensus that cisplatin-ineligible patients with locally advanced resectable disease should be referred for immediate RC.

What novel agents are being evaluated in the neoadjuvant setting?

VEGF inhibitors

As Hanahan and Weinberg summarized in their seminal review, sustained angiogenesis as a means of ensuring supply of oxygen and nutrients is one of the six hallmarks of cancer development and growth [55]. The incorporation of anti-angiogenic agents such as bevacizumab, a recombinant humanized monoclonal antibody that binds human VEGF, into chemotherapeutic regimens has improved survival outcomes in solid tumors, including advanced non-small-cell lung cancer and colon cancer [56,57]. Partly based on this efficacy, as well as the promising activity of bevacizumab in preclinical models of urothelial cancer cell lines [58–60] and the reported relationship between increased microvessel density and increased stage and decreased survival in UC [61], a number of trials have evaluated anti-VEGF therapy in this disease. A Phase II trial in advanced UC examined the combination of GC plus bevacizumab (GC-Bev) and found a median PFS, median OS, and overall response rate of 8.2 months, 19.1 months and 72%, respectively [62]. Based on these data, a randomized, double-blind, placebo-controlled Phase III trial is currently accruing to determine the role of first-line GC-Bev in advanced UC. Investigators are also studying the role of neoadjuvant bevacizumab in a number of small, single-institution trials. Interim results of a Phase II trial evaluating neoadjuvant GC-Bev followed by surgery and postoperative paclitaxel plus bevacizumab if persistent disease is evident on the pathological specimen provides some insight into the role of neoadjuvant anti-angiogenic therapy [63]. Thirteen patients with T2–4N0M0 disease received four cycles of GC-Bev (with bevacizumab administered at 15 mg/kg on day 1 of an every 21-day schedule) with four out of 13 (31%) patients demonstrating some degree of down-staging seen at RC (3/11 [27%] carcinoma *in situ* [pTis]). Postoperative complications were observed in five out of 12 (42%) patients and included enterovesical fistula (one patient), delayed wound healing (one patient), prolonged ileus (two patients) and pelvic abscess (one patient), all thought to be related to bevacizumab therapy. Another trial tested the addition of bevacizumab to DD-MVAC. In this single-institution, prospective, Phase II trial, 60 patients with UC (44 with bladder and 16 with upper tract) received DD-MVAC + bevacizumab (bevacizumab dosing not reported) [64]. The primary end point of ≤pT1N0M0 disease at surgery occurred in 53% of patients with 38% achieving pCR. The 2-year OS and disease-specific survival were 78 and 82%, respectively. This abstract did not comment on whether surgical complications associated with bevacizumab were observed.

Sunitinib, an oral multi-targeted receptor tyrosine kinase inhibitor with potent VEGF inhibition, also has documented single-agent activity in advanced bladder cancer [65]. The drug was also tested in combination with GC in the neoadjuvant setting with the primary end point of pCR. Although closed early due to incomplete accrual (18 out of planned 45 patients), one patient achieved a pCR (6.6%) and five patients (33%) had <pT2 disease; of these latter five patients, four exhibited pTis responses [66]. The authors concluded that sunitinib did not possess increased efficacy when added to GC in the neoadjuvant setting, although this observation was in the setting of suboptimal accrual. Due to the small size of these studies, no significant inferences can be made regarding the efficacy of anti-VEGF therapies in the neoadjuvant setting. The concerns over post-bevacizumab surgical complications are legitimate and will undoubtedly be a major factor in any future considerations for neoadjuvant therapy. Ultimately, however, the results of the Phase III trial of GC-bevacizumab in advanced disease will provide the rationale for further investigation of anti-VEGF therapy in the preoperative setting.

Other agents

Single-agent erlotinib, an oral epidermal growth factor receptor inhibitor, was evaluated in a small Phase II trial in patients with MIBC (clinical T2N0M0) with a primary outcome of pCR. In the 20 evaluable patients treated with erlotinib 150 mg daily for 4 weeks, five out of 20 patients (25%) experienced a pCR while seven out of 20 (35%) experienced ≤ pT1 response and an overall organ-confined response rate of 75% [67]. The most common side effect was rash; notably, every patient who exhibited any degree of disease down-staging also experienced a rash. Larger Phase II or confirmatory Phase III trials are required to define the effectiveness of erlotinib in the neoadjuvant setting and also to further explore the correlation between skin toxicity and response to therapy.

Similarly, dasatinib, an oral multi-targeted tyrosine kinase inhibitor of Src-mediated signaling, was studied in a Phase II neoadjuvant trial in patients unsuitable or unwilling to undergo cisplatin therapy. Patients received dasatinib 100 mg orally daily for 28 ± 7 days followed by RC 8–24 h after the last dose of treatment [68]. The primary end point was the feasibility of >60% of patients completing RC without dose-limiting toxicity. While the trial did reach its goal with 15 out of 25 patients (68%) completing surgical resection, pathological response was T1/Tis in three patients (14%) and ≥T2 in 19 patients (86%) with node-positive disease in six patients (27%).

Table 3 lists ongoing and completed clinical trials of novel agents in the neoadjuvant treatment of UC.

Table 3. Novel chemotherapeutic agents.

Regimen	Institution (location)	Patients (n)	Preliminary results	Ref.
DD-MVAC + BEV	MD Anderson (TX, USA)	60	pCR 38%, ≤ pT1 53%, 2-year OS 78%	[64]
GC-BEV	USCF (CA, USA)	15	pCR 0%, pTis 27%	[63]
GC-Sunitinib	MSKCC (NY, USA)	18	pCR 6.6%, stopped early due to incomplete accrual	[66]
Erlotinib	UNC – Chapel Hill (NC, USA)	20	pCR 25%, ≤pT1 35%, <pT2 75%	[67]
Dasatinib	Hoosier Oncology Group (IN, USA)	25	68% of patients completed surgery, pT1/pTcis 14%	[68]
GCa-Panitumumab	MSKCC	N/A	pCR (results pending)	
GC-Sorafenib	Tumor Institute (Italy)	N/A	pCR (results pending)	
Rapamycin	University of Texas – San Antonio (TX, USA)	N/A	Correlative (results pending)	
Cabazitaxel-C	United Bristol Healthcare (Bristol, UK)	N/A	Pathological response rate (results pending)	

A: Adriamycin (doxorubicin); BEV: Bevacizumab; C: Cisplatin; Ca: Carboplatin; DD: Dose-dense; MSKCC: Memorial Sloan-Kettering Cancer Center; M: Methotrexate; OS: Overall survival; pCR: Pathologic complete response; UNC: University of North Carolina; USCF: University California, San Francisco; V: Vinblastine.

Future perspective

Neoadjuvant chemotherapy represents a standard of care for the treatment of muscle-invasive urothelial cancer. Given the dismal prognosis of patients with advanced disease, the neoadjuvant setting represents a critical opportunity to prevent the development of metastatic UC and/or eradicate pre-existing micrometastases. Unfortunately, in the USA, the National Cancer Database estimates 13% of eligible patients received NAC in 2007 [69]. In Europe, the numbers are even lower with a reported 13% of potentially eligible patients even assessed for NAC, with less undoubtedly receiving treatment [70]. Studies are also underway to identify whether molecular profiles or biologic markers could identify which patients are more likely to respond or should be excluded from NAC based on predicted resistance [71]. One such approach is the coexpression extrapolation (COXEN) methodology which utilizes gene expression models derived from *in vitro* drug testing of established cell line panels, such as the NCI-60, to generate predictive biomarkers of response to standard chemotherapy [72]. This approach has been validated in two cohorts of patients with bladder cancers from clinical trials for which expression array data were available, one cohort treated with neoadjuvant chemotherapy and one treated for more advanced disease. Notably, COXEN scores predicted sensitivity to MVAC in the neoadjuvant cohort with a positive predictive value of 71% and a negative predictive value of 78% [73]. Investigators will attempt to prospectively validate this predictive biomarker by incorporating a COXEN analysis into a planned SWOG randomized Phase II trial comparing neoadjuvant DD-MVAC and GC. This Phase II intergroup trial seeks:

- To validate prospectively the accuracy of the COXEN biomarker in predicting the pathological response of bladder tumors to the designated regimen, either GC or DD-MVAC; and
- To provide the first direct comparison of outcomes (response and toxicity) between the DD-MVAC and standard-dose GC regimens in the neoadjuvant setting.

If successful, COXEN could represent a patient-specific biomarker predictive of response to neoadjuvant treatment and survival.

Given the survival data presented above and the improved tolerability of neoadjuvant chemotherapy regimens, it is our institutional approach that all patients with muscle-invasive or locally advanced urothelial cancer are assessed for and recommended NAC when eligible. It is our opinion that a meaningful impact on survival could be achieved for patients with muscle-invasive UC if this approach were to be adopted universally. Ultimately, the integration of novel chemotherapeutic and targeted therapies into the neoadjuvant setting will hopefully improve current survival rates observed with standard neoadjuvant chemotherapeutic regimens in UC.

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Executive summary

- Improved pathologic response (less invasive disease) to neoadjuvant chemotherapy is associated with more favorable long-term survival.
- Cisplatin-based neoadjuvant chemotherapy is the standard of care in eligible patients with muscle-invasive bladder cancer.
- Neoadjuvant regimens of choice include methotrexate, vinblastine, doxorubicin, cisplatin (MVAC) or gemcitabine, cisplatin (GC).
- Accelerated dosing regimens offer the possibility of improved outcomes as compared with standard dose chemotherapy, but definitive trials are still pending.
- Neoadjuvant chemotherapy for upper tract disease is still considered investigational at this time with clinical trials regarding its use currently pending.
- Non-cisplatin-based chemotherapy regimens have reduced efficacy as compared with cisplatin-based regimens in the neoadjuvant setting.
- In cisplatin-ineligible patients, radical cystectomy and bilateral pelvic lymph node dissection remain the standard of care.
- The use of novel agents, including anti-VEGF therapy and EGFR inhibition, in combination with standard chemotherapy in the neoadjuvant setting is investigational at this time.

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