Neoadjuvant chemotherapy is underutilized in muscle-invasive bladder cancer.

Role of Systemic Chemotherapy in Urothelial Urinary Bladder Cancer

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Background: Radical cystectomy is the standard of care for patients with localized muscle-invasive bladder cancer; however, 50% of patients still relapse in distant sites following surgery. A systemic approach is needed to improve outcomes in bladder cancer in the metastatic and perioperative settings.

Methods: We reviewed the literature for use of systemic chemotherapy in bladder cancer and its role in metastatic, neoadjuvant, and adjuvant settings, including patients with comorbidities and renal dysfunction. Current controversies on the role of chemotherapy in neoadjuvant and adjuvant settings as well as the role of novel agents are discussed.

Results: First-line cisplatin-based polychemotherapy improves survival in the metastatic setting and is the standard of care. Approved regimens for subsequent-line therapy do not exist. Chemotherapy has a modest benefit in the neoadjuvant setting, but evidence is insufficient to justify its role in the adjuvant setting despite a possible benefit. Carboplatin cannot be substituted for cisplatin in fit patients, and the addition of taxane to a standard regimen cannot be recommended.

Conclusions: Systemic chemotherapy plays a central role in the management of invasive bladder cancer in the metastatic and neoadjuvant settings, but its role in the adjuvant setting remains undefined. Neoadjuvant chemotherapy is underutilized and should be routinely used. Pathological downstaging strongly correlates with improved outcomes and may serve as a surrogate end point for survival. An urgent need exists for the development of novel therapeutic agents to improve outcomes.

Introduction
Bladder cancer is the fourth most common cancer in men in the United States, and approximately 72,570 new cases and 15,210 deaths will occur in men and women in 2013 due to this disease.¹

Although the majority of patients with bladder cancer present with noninvasive bladder cancer, 20% to 40% patients present with more advanced disease or progress following treatment for superficial disease.² The gold standard of treatment for clinically localized invasive bladder cancer is radical cystectomy and, depending on the extent of primary tumor, nodal status,
and extent of surgery, around 50% patients still relapse after surgery, most commonly in distant sites.5,5

Combination systemic chemotherapy is widely used for locally advanced and metastatic bladder cancer. Its use in neoadjuvant fashion improves survival in patients with muscle-invasive bladder cancer,6 and benefit may also exist in adjuvant chemotherapy following cystectomy in patients at high risk for relapse. It is imperative to develop optimal, less toxic chemotherapy regimens by incorporating novel targeted agents to improve outcomes in bladder cancer.

Chemotherapy for Metastatic Bladder Cancer

Typically, bladder cancer recurs in the pelvic lymph nodes and distant sites. Despite the fact that bladder cancer is chemosensitive, the prognosis of patients with metastatic disease remains poor, with a median survival of 14 months and a 5-year survival rate of 15%.7 Single-agent use of various chemotherapeutic agents such as methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) was first shown to be effective for bladder cancer in 1987, but the use of these single agents has been limited by low, short-lived response rates, with few complete responses and the median survival between 4 to 6 months.8,9 The need to improve outcomes in metastatic bladder cancer has led to the development of combination chemotherapy regimens.

First-line Chemotherapy

Cisplatin-containing combination chemotherapy has been widely used for more than 20 years.10 Results of a combination of MVAC were first reported in 1985 and showed that, although the overall response rate was 70%, the median survival was 13 months and 24% patients achieved long-term disease-free survival.11 A phase III intergroup study compared the efficacy of single-agent cisplatin with MVAC in 269 patients with metastatic or locally advanced urothelial cancer.12,13 The response rate (39% vs 12%) and OS (12.5 vs 8.2 months) were significantly higher in patients receiving MVAC; however, this regimen was associated with increased toxicity, including mucositis, neutropenia, infections, gastrointestinal complications, and a toxic death rate of 3% to 4%. A small fraction of patients received full-dose MVAC without dose modifications. While long-term follow-up results of this trial confirmed the original findings that MVAC was superior to cisplatin alone, durable progression-free survival was rare and seen in less than 4% of patients. MVAC was also demonstrated to be superior to a combination chemotherapy regimen of cisplatin, cyclophosphamide, and doxorubicin (CISCA) in a randomized trial of 110 patients.14 The median OS in patients treated with MVAC was 48.3 weeks compared with 36.1 weeks in patients treated with CISCA. In an attempt to improve efficacy of the MVAC regimen, a phase III randomized trial was undertaken by Sternberg et al15 that assigned 263 patients to high-dose-intensity MVAC (HD-MVAC; 2-week cycle) with granulocyte colony-stimulating factor (G-CSF) and standard MVAC (4-week cycle). HD-MVAC was associated with higher complete response rates (21% vs 9%) and longer progression-free survival (9.1 vs 8.2 months), but no significant difference was found in OS rates between the two groups (P = .122). Although the incidences of grades 3 to 4 neutropenia and mucositis were significantly lower with HD-MVAC, they were still associated with a toxic death rate of 3%. In the 7-year updated analysis, a borderline significant survival benefit was seen with HD-MVAC.16 The 5-year survival rate was 21.8% in the HD-MVAC arm compared with 13.5% in the MVAC arm (hazard ratio [HR] = 0.76; 95% confidence interval [CI], 0.58–0.99; P = .042). MVAC with G-CSF was also found to be superior to combination docetaxel/cisplatin (DC) therapy with G-CSF, and it was also associated with a lower toxicity rate than reported for MVAC without G-CSF.17 The substantial toxicity of the MVAC regimen is especially concerning for the elderly who may have multiple pre-existing comorbidities, a patient population that comprises a significant proportion of patients with bladder cancer. Therefore, a need exists to develop newer combination chemotherapy regimens with better toxicity profiles and equivalent or better efficacy than the MVAC regimen. Based on the promising clinical activity of combination gemcitabine/cisplatin (GC),18,20 a phase III randomized trial of 405 patients was conducted to compare GC with MVAC.7,21 The response rates (49% vs 46%), time to progression (median: 7.4 vs 7.4 months), and OS rates (median OS 13.8 vs 14.8 months; P = .75) were similar in both arms. Notably, this trial was not designed as an equivalence trial but rather to detect a 35% difference in the survival rates between the two arms. The updated analysis confirmed the expected equivalence of these two regimens with an HR of 1.09 (95% CI, 0.88–1.34; P = .66).7 More importantly, GC was better tolerated than MVAC, with 63% of cycles administered with no dose modifications compared with 37% dose modifications in the MVAC arm. Patients on the GC arm experienced less grade 3 or 4 neutropenia (71% vs 82%), neutropenic fever (2% vs 14%), and neutropenic sepsis (1% vs 12%), and grade 3 or 4 mucositis was significantly less common on the GC arm (1% vs 22%), as was the toxic death rate (1% vs 3%). The equivalent efficacy and better tolerability profile of the GC regimen has led to its adoption as the preferred, standard first-line treatment for patients with locally advanced or metastatic bladder cancer in the United States. Data from studies of randomized trials of chemotherapy for metastatic bladder cancer are presented in Table 1.7,12,14,15,17,19,21,22
Various studies have tested a three-drug combination using platinum and taxanes with varying response rates to determine if the addition of a third cytotoxic agent with a different mechanism of action but without an overlapping toxicity with GC would further improve the efficacy of GC. The combination of paclitaxel, gemcitabine, and cisplatin (PGC) showed an overall response rate of 77.6%, with a 27.6% complete response rate and a median survival of 15.6 months. Based on these encouraging results, Bellmunt et al compared these two regimens in a phase III study of 607 patients. The overall response rate was higher among patients treated with PGC than those treated with GC (55.5% vs 43.6%; \(P = .0031\)). Although the median OS was 3.1 months longer in the PGC arm (15.8 vs 12.7 months), it was not statistically significant (HR = 0.85; 95% CI, 0.72–1.02; \(P = .075\)). Moreover, patients in the PGC arm experienced more instances of grade 3 and 4 neutropenia. Based on the results of this randomized phase III trial that addressed the efficacy of three cytotoxic drugs compared with only two drugs, currently no role exists for the addition of a third agent to the GC combination.

Carboplatin has been substituted for cisplatin for many other cancers to provide an equivalent efficacy rate and better tolerability. However, its substitution as first-line chemotherapy in place of cisplatin for patients with bladder cancer who are otherwise eligible or “fit” to receive cisplatin is not well studied. Although some phase II studies reveal that carboplatin is inferior to cisplatin, there exists one phase III trial that compared MVAC to carboplatin/paclitaxel and showed a trend toward worse survival in the carboplatin arm, although this result was not significant. However, the study was closed early and no definite conclusions can be drawn. The criteria for defining patients as unfit for cisplatin, as proposed by a consensus working group, include a performance status of 2 or higher, a creatinine clearance of less than 60 mL/minute, hearing loss of 25 dB at two contiguous frequencies, grade 2 or higher peripheral neuropathy, or New York Heart Association Class III or higher heart failure. The use of carboplatin in place of cisplatin is not recommended as first-line chemotherapy for patients with normal renal function; by contrast, it should be considered in patients with decreased creatinine clearance or any of the above-mentioned criteria.

### Second-line Chemotherapy

No standard second-line chemotherapy exists for patients with bladder cancer who progress on the standard first-line platinum-based treatment with MVAC or GC. For selected patients who progress on first-line cisplatin-based chemotherapy and are still eligible for cisplatin treatment, rechallenge with cisplatin-containing chemotherapy is feasible, depending on their initial response. Han et al studied the efficacy of MVAC in patients who failed GC in a small phase II study of 30 patients. The overall response rate was 30%, with a 6.7% complete response rate, and 7 out of 16 patients who previously responded to GC had a response to MVAC, while 2 out of 14 who had not responded to GC showed a response to MVAC.

Various single agents, including paclitaxel, docetaxel, gemcitabine, ifosfamide, oxaliplatin, and vinflunine, have been studied in this setting with modest response rates of less than 20%. Of these, the largest single-agent trial with 370 patients utilized vinflunine, a novel vinca alkaloid that showed a response rate of 9% and a small but significant OS benefit over best supportive care (6.9 vs 4.6 months; \(P = .04\)). It had a tolerable safety profile and became the first approved second-line chemotherapy agent in Europe for metastatic bladder cancer, but it is not yet available in the United States.
Pemetrexed, a multitargeted antifolate, is also an active agent in the second-line setting. The Hoosier Oncology Group study demonstrated a response rate of 28% and a median survival of 9.6 months with single-agent pemetrexed in previously treated patients with urothelial cancer. Albumin-bound paclitaxel is another agent that has shown promising activity in a phase II study in 48 patients progressing on platinum-based chemotherapy. Among 47 evaluable patients, partial responses were seen in 15 patients (32%) and stable disease in 10 (21%), with an overall disease control rate of 53%. Eribulin has demonstrated response rates of 40% as a single agent in bladder cancer, including in patients who had received neoadjuvant chemotherapy. Moreover, it is not renally excreted and is being studied in patients with renal dysfunction (NCT00365157).

Various combination chemotherapy regimens have also been studied in this setting with reasonable response rates. Although no preferred regimen exists, most studies have combined gemcitabine with another agent. A gemcitabine/paclitaxel doublet has been extensively studied in many phase II trials, with response rates in the range of 30% to 60%. Notably, different dosing schedules were used in these studies. Although no consensus exists on the preferred schedule, a small study by Fechner et al comparing biweekly and 3-weekly dosing reported that the 3-weekly schedule was associated with higher response rates. A phase III trial of around 100 patients compared short-term use (6 cycles) vs prolonged use (until progression) of gemcitabine and paclitaxel given 3 times weekly. Prolonged treatment did not improve outcomes and was associated with significant toxicity, including 2 toxic deaths. However, the short-term use of this regimen was associated with a high response rate of 40%, making it a promising second-line treatment option for patients with metastatic disease.

**Neoadjuvant Chemotherapy**

Approximately 50% of patients with invasive bladder cancer develop distant metastases following radical cystectomy alone. Neoadjuvant chemotherapy for bladder cancer offers several potential advantages. It may be better tolerated as opposed to the post-cystectomy setting in which a delay may be possible due to complications from surgery. Micrometastatic disease, if present, is treated earlier. Downstaging of the tumor may also result in making the tumor more amenable to resection with negative margins and, in very selected cases, bladder preservation may be feasible, depending on response to chemotherapy, although this therapy requires testing in a randomized trial. Lastly, neoadjuvant chemotherapy allows the assessment of response upfront and the determination about whether the tumor is responsive to a particular chemotherapy. Conversely, many believe that neoadjuvant chemotherapy might potentially delay the definitive treatment of bladder cancer. The tumor may progress while on treatment if it is resistant to chemotherapy. Discrepancies between clinical and pathological stages have been observed in 30% of cases, making it difficult to assess tumor response following chemotherapy. This is because patients who are clinically staged and cured with surgery alone may receive overtreatment. The role of neoadjuvant chemotherapy for bladder cancer has been tested in randomized clinical trials, but most of these studies were underpowered to detect a difference in survival outcomes. Moreover, the quality of surgery is a confounding factor in many studies. Initial studies were conducted using the single agent cisplatin, which did not render any clinical benefit; however, recent trials have included combination cisplatin-based regimens demonstrating either no survival benefit or a trend toward a marginal survival benefit, with the exception of the European Organization for the Treatment and Cure of Cancer (EORTC)/Medical Research Council (MRC) trial (Table 2). The EORTC/MRC trial is the largest randomized trial of neoadjuvant chemotherapy in bladder cancer evaluating the role of 3 cycles of neoadjuvant cisplatin, methotrexate, and vinblastine (CMV) chemotherapy prior to local radical treatment consisting of radiation therapy or cystectomy. The trial recruited 976 patients, of which 491 patients were assigned to chemotherapy arm and 80% of those completed 3 cycles of chemotherapy. The chemotherapy-related mortality rate was 1%. At the time of first analysis (with a median follow-up of 4 years), a trend was seen toward survival benefit, with an HR of 0.85 (95% CI, 0.71–1.02; \( P = .075 \)), which translated into a statistically nonsignificant absolute benefit of 5.5% in the 3-year survival rate favoring patients in the chemotherapy group. The updated results published in 2011 demonstrated a 16% reduction in the risk of death after neoadjuvant chemotherapy (HR = 0.84; 95% CI, 0.72–0.99; \( P = .037 \)). The estimated 10-year survival was 36% in the chemotherapy group and 30% in the control arm. These results suggest that a small survival benefit of approximately 6% was maintained over time. The role of neoadjuvant CMV was evaluated in a randomized trial conducted by the Radiation Therapy Oncology Group (RTOG 89-03). The study population consisted of 126 patients with stage T2–T4aNxM0 bladder cancer. Patients were randomized to receive or not receive 2 cycles of CMV followed by concurrent cisplatin and pelvic irradiation. Cystectomy was recommended for patients who achieved less than a clinical complete response. The trial was closed early due to an unexpected high rate of severe neutropenia and sepsis, with 3 toxic deaths from neutropenic sepsis during induction chemotherapy,
and no survival difference was observed between the two groups.

An intergroup trial initiated by SWOG\textsuperscript{61} recruited 317 patients from 1987 to 1998 and evaluated the benefit of neoadjuvant chemotherapy combination of MVAC in patients with cT2–T4aN0M0 bladder cancer. The planned radical cystectomy was performed in 82% of the patients randomized to the chemotherapy arm. The mean time to surgery was 115 days following randomization. The 5-year OS rates were 57% and 43% in the neoadjuvant chemotherapy and cystectomy-only groups, respectively, but these results did not reach statistical significance ($P = .06$). In the MVAC group, 38% of patients had no residual disease at the time of cystectomy compared with 15% of patients in the cystectomy group ($P < .001$). At 5 years, more than 80% of patients who achieved pT0 at the time of surgery were alive compared with approximately 40% of patients with residual disease at cystectomy, suggesting the pathological downstaging was associated with improved outcomes. A cooperative group in Italy\textsuperscript{56} also conducted a trial of 206 patients exploring the role of neoadjuvant MVAC prior to cystectomy and demonstrated no significant difference in survival. The 3-year survival rate was 62% for patients receiving preoperative MVAC and 68% for patients undergoing cystectomy alone.

The Nordic cystectomy I trial\textsuperscript{58} involving 325 patients evaluated neoadjuvant doxorubicin and cisplatin prior to radiation therapy and cystectomy vs radiation therapy and cystectomy only. The Nordic cystectomy II trial\textsuperscript{59} randomized 317 patients to preoperative methotrexate and cisplatin vs cystectomy alone. Both of these trials demonstrated a trend toward survival benefit with chemotherapy that was not statistically significant. The combined analysis of the two trials demonstrated a 20% reduction in the risk of death, with an HR of 0.80 (95% CI, 0.64–0.99) and an absolute risk reduction of 8% at 5 years, with survival rates of 56% in the neoadjuvant chemotherapy group vs 48% in the control group.\textsuperscript{64}

Because most of these trials demonstrated inconclusive results and were of modest size, several meta-analyses have been conducted to reliably assess the value of neoadjuvant chemotherapy in bladder cancer. The Advanced Bladder Cancer Meta-analysis Collaboration\textsuperscript{65} reported a meta-analysis in 2003 that included 2,688 individual patient data from 10 randomized trials. The data from the SWOG trial were not available for this analysis. The pooled analysis from the nine trials with available survival data demonstrated no statistically significant difference in OS, with an HR of 0.91 (95% CI, 0.83–1.01). However, when the trials incorporating single-agent cisplatin were excluded, the HR was 0.87 (95% CI, 0.78–0.97; $P = .016$), and a statistically significant absolute benefit of 5% at 5 years was seen, with survival improvement from 45% to 50%. The same group updated the results to

### Table 2. — Selected Randomized Trials of Neoadjuvant Chemotherapy in Bladder Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>Stage</th>
<th>Experimental Arm</th>
<th>Control Arm</th>
<th>Survival Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>WMURG/ABC5\textsuperscript{41}</td>
<td>255</td>
<td>T2–T4NxM0</td>
<td>Cis + RT</td>
<td>RT</td>
<td>No difference</td>
</tr>
<tr>
<td>Coppin\textsuperscript{52}</td>
<td>99</td>
<td>T2–T4bN0–3M0</td>
<td>Cis + RT/S</td>
<td>RT/RT + S</td>
<td>3-yr OS: 47% vs 33% ($P = .34$)</td>
</tr>
<tr>
<td>CUETO\textsuperscript{53}</td>
<td>122</td>
<td>T2–T4aNx–N2M0</td>
<td>Cis + S</td>
<td>S</td>
<td>6.5-yr OS: 35.5% vs 37.3% ($P = .95$)</td>
</tr>
<tr>
<td>EORTC/MRC\textsuperscript{54,65}</td>
<td>976</td>
<td>T2G3–T4aNxM0</td>
<td>CMV + S/RT</td>
<td>S/RT</td>
<td>10-yr OS: 36% vs 30% ($P = .037$)</td>
</tr>
<tr>
<td>GUONE\textsuperscript{66}</td>
<td>206</td>
<td>T2–T4N0M0</td>
<td>MVAC + S</td>
<td>S</td>
<td>5-yr OS: 55% vs 54% ($P = NS$)</td>
</tr>
<tr>
<td>GISTV\textsuperscript{57}</td>
<td>171</td>
<td>T2–T4N0M0</td>
<td>MVEC + S</td>
<td>S</td>
<td>Median OS: NR vs 5.5 yrs ($P = NS$)</td>
</tr>
<tr>
<td>Nordic I\textsuperscript{68}</td>
<td>325</td>
<td>T1G3–T4aNxM0</td>
<td>CA + RT + S</td>
<td>RT + S</td>
<td>5-yr OS: 59% vs 51% ($P = .1$)</td>
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<tr>
<td>Nordic II\textsuperscript{59}</td>
<td>317</td>
<td>T2–T4aNxM0</td>
<td>CM + S</td>
<td>S</td>
<td>5-yr OS: 53% vs 46% ($P = .24$)</td>
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<tr>
<td>Daveca 89-01\textsuperscript{60}</td>
<td>33</td>
<td>T2–T4bNx–3M0</td>
<td>CM + S</td>
<td>S</td>
<td>5-yr OS: 64% vs 46% ($P = .76$)</td>
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<tr>
<td>Daveca 89-02\textsuperscript{60}</td>
<td>120</td>
<td>T2–T4bNx–3M0</td>
<td>CM + RT</td>
<td>RT</td>
<td>5-yr OS: 19% vs 24% ($P = .98$)</td>
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<tr>
<td>SWOG\textsuperscript{61}</td>
<td>317</td>
<td>T2–T4aN0M0</td>
<td>MVAC + S</td>
<td>S</td>
<td>5-yr OS: 57% vs 43% ($P = .06$)</td>
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<tr>
<td>Abol-Eneim\textsuperscript{61}</td>
<td>196</td>
<td>T2NkM0</td>
<td>CaMV + S</td>
<td>S</td>
<td>5-yr DFS: 82% vs 42% ($P = .013$)</td>
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<tr>
<td>RTOG 89-03\textsuperscript{62}</td>
<td>126</td>
<td>T2–T4aNxM0</td>
<td>CMV + RT/Cis + S (if &lt; CR)</td>
<td>RT/Cis + S (if &lt; CR)</td>
<td>5-yr OS: 48% vs 49% ($P = NS$)</td>
</tr>
</tbody>
</table>

CaMV = carboplatin, methotrexate, and vinblastine, CA = cisplatin and doxorubicin, Cis = cisplatin, CM = cisplatin/methotrexate, CMV = cisplatin, methotrexate, and vinblastine, CR = complete response, DFS = disease-free survival, MVAC = methotrexate, vinblastine, doxorubicin, and cisplatin, MVEC = methotrexate, vinblastine, epirubicin, and cisplatin, NR = no response, NS = not significant, OS = overall survival, RT = radiation therapy, S = surgery.
incorporate 3,005 patients from 11 randomized trials, finding that neoadjuvant combination platinum-based chemotherapy was associated with a significant survival benefit (HR = 0.86; 95% CI, 0.77–0.95; \(P = .003\)), which was equivalent to a 5% absolute improvement in survival at 5 years.66

A similar meta-analysis was performed by the Cancer Care Ontario in Canada and included 2,605 patients from 11 trials.67 The pooled HR for survival was 0.90 (95% CI, 0.82–0.99; \(P = .02\)). When eight trials using cisplatin-based combination chemotherapy were included, the pooled HR was 0.87 (95% CI, 0.78–0.96; \(P = .006\)), which was consistent with an absolute OS benefit of 6.5% (95% CI, 2–11) from 50% to 56.5%.

The results of the above trials and meta-analyses suggest that neoadjuvant chemotherapy is well tolerated and associated with a survival benefit of 5% to 6% in patients and pathological complete response rates of 30% to 40%, which, in turn, help predict more accurate survival outcomes. By contrast, even with a high rate of complete pathological response with neoadjuvant chemotherapy, the survival benefit is not dramatic when compared with patients who undergo surgery alone and have no evidence of disease, possibly suggesting that micrometastatic disease is an early event in invasive bladder cancer and chemotherapy might not effectively eradicate it. Regardless, given the benefit associated with neoadjuvant chemotherapy, it should be considered as the standard of care for patients with invasive bladder cancer.

In clinical practice, neoadjuvant chemotherapy is sometimes utilized for patients with node-positive disease, limited metastatic disease, or both. Although it may be appropriate to offer neoadjuvant chemotherapy as preoperative or palliative chemotherapy prior to surgery in selected patients who are young and have an excellent performance status, it should be noted that the neoadjuvant clinical trials did not include patients with N+ and/or M+ disease. Patients with N+ and/or M+ disease must be counseled to avoid unrealistic expectations with neoadjuvant chemotherapy because they are at high risk of having persistent disease at the time of cystectomy and may then also require adjuvant chemotherapy.

**Pathological Downstaging**

Pathological tumor stage following radical cystectomy strongly predicts patient outcomes and may serve as a potential surrogate marker for OS rates.68,69 Rates of pathological downstaging to pT0 at cystectomy without neoadjuvant therapy range from 6% to 15% and up to 38% with neoadjuvant chemotherapy.47,61,68

Tollefson et al68 reviewed the long-term outcomes in 1,177 patients with muscle-invasive urothelial carcinoma at a single institution who underwent radical cystectomy without neoadjuvant therapy. They observed that pathological tumor stage strongly correlated with disease recurrence and cancer-specific mortality. The 10-year cancer-specific survival rates were 84.1%, 77.4%, 71.1%, and 58.5% for patients with pT0, pTis, pT1, and pT2 tumors, respectively. Patients with residual muscle-invasive disease had higher rates of bladder cancer-specific and overall mortality compared with those with residual nonmuscle invasive disease (< pT2). Even among patients with residual nonmuscle invasive disease, those with pTis and pT1 tumors had higher rates of disease progression compared with those with pTa and pT0 disease.

The landmark intergroup trial that compared neoadjuvant chemotherapy with MVAC followed by cystectomy to cystectomy alone showed that, in both groups, improved survival rate was associated with pT0 disease at cystectomy.61 The 5-year survival rates were 85% for the group that received neoadjuvant chemotherapy and 82% for the control group. Neoadjuvant chemotherapy significantly increased the rates of pathological downstaging of tumor to pT0 (38% vs 15%; \(P < .001\)), thus indicating that that survival benefit of neoadjuvant chemotherapy was strongly related to pathological downstaging of tumor to pT0.

In the post-hoc analysis of the combined Nordic Cystectomy Trials I and II to evaluate the effect of neoadjuvant chemotherapy on tumor downstaging and OS rate, a survival benefit was seen with chemotherapy-induced downstaging.69 The rate of complete downstaging (CD; pT0N0) was almost double in the neoadjuvant chemotherapy arm compared with the control arm (22.7% vs 12.5%; \(P = .006\)). The rates of noninvasive downstaging (pT0/pTis/pTaN0) were also significantly increased with neoadjuvant chemotherapy. At 5 years, an absolute risk reduction of 31.1% was seen in OS rates for the neoadjuvant chemotherapy-induced CD group compared with the control group (\(P = .001\)) and an absolute risk reduction of 17.9% for the neoadjuvant chemotherapy-induced noninvasive downstaging group. These results further confirm that neoadjuvant chemotherapy increases tumor downstaging rates, which, in turn, are associated with a survival benefit. Pathological downstaging may represent a new outcome and point of prognosis for clinical trials in bladder cancer utilizing neoadjuvant chemotherapy. Moreover, this end point may help identify patients who are resistant to standard chemotherapy and who may benefit from a patient-tailored approach using novel targeted therapies based on the molecular characteristics of their tumors.

**Adjuvant Chemotherapy**

The rationale of adjuvant chemotherapy in bladder cancer is to delay recurrence and prolong survival in patients with nonorgan-confined disease (pT3–
T4, N0 or N+) as this group has a high likelihood of recurrence with cystectomy alone. The 5-year recurrence-free survival rate is in the range of 30% for node-positive disease and 50% for pT3 to T4 disease.47,70 Adjuvant chemotherapy allows immediate local treatment, avoiding delay in treatment for patients with chemotherapy-resistant tumors, and it may also help avoid overtreatment based on inaccurate clinical staging. However, in the postoperative setting, many patients may not receive chemotherapy due to complications. A few randomized trials address its utility; however, available trials are limited due to small numbers. In a comparative nonrandomized trial first reported by Logothetis et al,71 71 patients with high risk for relapse (nodal metastases, extravesicular involvement, lymphatic/vascular invasion, or pelvic visceral invasion) received adjuvant CISCA chemotherapy following cystectomy, while 62 patients with similar high risk for relapse did not. At a mean follow-up of 118 weeks, a significant survival advantage was seen in this group of patients receiving adjuvant chemotherapy compared with those who had unfavorable pathological findings and did not receive adjuvant chemotherapy (70% vs 37%; P = .00012). However, no benefit was seen in patients with favorable pathological findings who underwent adjuvant chemotherapy following cystectomy.

In a Swiss study by Studer et al72 involving 77 patients, adjuvant use of single-agent cisplatin failed to show a survival benefit compared with radical cystectomy alone. The first prospective randomized phase III trial that showed a survival benefit with adjuvant chemotherapy was reported by Skinner et al,73 in which 91 patients with invasive T3 to T4 or N+ disease were assigned to adjuvant chemotherapy with a cisplatin-containing combination regimen or observation alone. Time to progression was significantly delayed in the chemotherapy group, with 70% of the patients being free of disease at 3 years compared with 46% in the observation group. The median survival for patients in the chemotherapy group was 4.3 years compared with 2.4 years in the observation group (P = .0062), and the extent of lymph node involvement was found to be the most important prognostic variable. However, one of the shortcomings of this trial was that 25% of patients assigned to the chemotherapy group did not receive any chemotherapy. Furthermore, the regimen used was not consistent. In a German trial by Stockle et al,74 49 patients with pT3b, pT4a, and/or pelvic lymph node involvement were randomized to receive 3 adjuvant cycles of MVAC or epirubicin (MVEC) following radical cystectomy or no adjuvant chemotherapy. Of the 26 patients randomized to the chemotherapy group, 18 received treatment, and, of those, 3 had tumor progression compared with 18 of the 23 patients in the control group. The study was stopped early due to these results. Additional patients were then recommended routine adjuvant chemotherapy and updated results were reported.75 Of the collective total of 83 patients, 38 had received adjuvant chemotherapy and 45 did not. A marked prognostic advantage was seen in favor of patients undergoing adjuvant chemotherapy; the 5-year progression-free survival rate was 59% after the recommendation to

### Table 3. — Selected Randomized Trials of Adjuvant Chemotherapy in Bladder Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>Experimental Arm</th>
<th>Control Arm</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studer72</td>
<td>77</td>
<td>Cis</td>
<td>Surgery</td>
<td>No benefit</td>
</tr>
<tr>
<td>Skinner73</td>
<td>91</td>
<td>Cis-containing combination chemotherapy</td>
<td>Surgery</td>
<td>Benefit, DFS (4.3 vs 2.4 yrs) No OS benefit</td>
</tr>
<tr>
<td>Stockle74,76</td>
<td>49</td>
<td>MVAC/MVEC</td>
<td>Surgery</td>
<td>Benefit, tumor-specific survival (71.8 vs 20.4 mos), PFS (66.9 vs 11.6 mos) No chemotherapy at time of relapse</td>
</tr>
<tr>
<td>Cognetti80</td>
<td>193</td>
<td>GC</td>
<td>Surgery</td>
<td>No benefit Closed early</td>
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<td>SOGUG81</td>
<td>142</td>
<td>PGC</td>
<td>Surgery</td>
<td>Benefit OS (60% vs 31%)</td>
</tr>
<tr>
<td>Bono79</td>
<td>83</td>
<td>CM</td>
<td>Surgery</td>
<td>No benefit</td>
</tr>
<tr>
<td>Freiha78</td>
<td>50</td>
<td>CMV</td>
<td>Surgery</td>
<td>Benefit, TTP (37 vs 12 mos) Closed early No OS benefit</td>
</tr>
</tbody>
</table>

Cis = cisplatin, CM = cisplatin/methotrexate, CMV = cisplatin, methotrexate, and vinblastine, DFS = disease-free survival, GC = gemcitabine/cisplatin, MVAC = methotrexate, vinblastine, doxorubicin, and cisplatin, MVEC = MVAC or epirubicin, OS = overall survival, PFS = progression-free survival, PGC = paclitaxel, gemcitabine, and cisplatin, TTP = time to progression
receive chemotherapy compared with 13% after a recommendation of cystectomy alone. Long-term survival data in the initial 49 patients were reported by this group, with a median follow-up of 160 months. The median progression-free survival was 66.9 months with adjuvant chemotherapy compared with 11.6 months with observation alone ($P = .002$) and tumor-specific survival was 71.8 compared with 20.4 months ($P = .007$) favoring adjuvant treatment. Notably, patients randomized to observation after cystectomy were not given chemotherapy at the time of relapse. However, in another contemporary German series, adjuvant MVEC did not improve survival when compared with cystectomy alone. In another trial, 55 patients with pT3b, T4, or N+ disease were randomized to observation or adjuvant chemotherapy with CMV. Adjuvant chemotherapy was associated with a longer time to progression but no improvement was seen in OS rates. Adjuvant cisplatin/methotrexate also failed to demonstrate a survival advantage. The results from these trials were inconclusive because the studies were small and underpowered or were closed early due to poor accrual or interim analyses.

Several large randomized trials focusing on adjuvant chemotherapy in bladder cancer have been reported (Table 3), but many closed prematurely due to poor accrual as well. An Italian multicenter trial, reported in abstract form, randomized 193 patients with pT2 grade 3, pT3-4 N0-2 urothelial carcinoma to adjuvant GC vs chemotherapy at relapse and failed to show a significant difference in survival. However, it accrued only 32% of the target sample size and was closed early. The Spanish Oncology Genitourinary Group 99/01 study planned to randomize patients with T3/T4 or N+ urothelial carcinoma to paclitaxel, gemcitabine, and cisplatin (PGC) vs observation. This trial was terminated due to poor accrual as only 142 patients were enrolled instead of the planned target of 340. The results were reported in abstract form. With a median follow-up of 51 months, improvement in the 5-year OS rate was seen with chemotherapy (60% vs 31%; $P < .0009$). The EORTC conducted a phase III trial (NCT00028756) comparing immediate vs deferred chemotherapy with MVAC, HD-MVAC with growth factor support, or GC after radical cystectomy in patients with pT3–4 or N+ urothelial carcinoma. However, the trial was closed after 7 years due to poor accrual, and no results are available. The Cancer and Leukemia Group B also attempted to compare sequential chemotherapy with gemcitabine and doxorubicin followed by paclitaxel and cisplatin vs GC alone as adjuvant therapy following cystectomy, but the trial was closed due to poor accrual (NCT00014534).

Based on the available evidence, no definite recommendations can be made regarding the role of adjuvant chemotherapy for patients with locally advanced bladder cancer following cystectomy, even though the meta-analysis of the available randomized controlled trials suggests a 25% relative reduction in the risk of death with adjuvant chemotherapy. However, the power of the meta-analysis is limited and does not provide enough evidence to make any recommendations. Currently, no role of adjuvant chemotherapy exists in patients not considered at high risk for relapse (tumors pT2 or less, no nodal involvement or lymphovascular invasion), but adjuvant chemotherapy may be considered for patients at high risk for relapse, especially if no neoadjuvant chemotherapy was given.

Overexpression of p53 has been suggested to be a prognostic marker for recurrence in bladder cancer, but sufficient evidence to support this suggestion is lacking. In a cooperative group trial, patients with T1/T2N0M0 urothelial bladder cancer who underwent cystectomy were tested for p53 expression. Those with p53-positive tumors were randomized to adjuvant MVAC chemotherapy vs observation, while those with p53-negative tumors were observed. Neither the prognostic value of p53 nor the benefit of MVAC chemotherapy in patients with p53-positive tumors was confirmed, and the trial was terminated after an interim futility analysis. However, more studies are needed to test its predictive value in higher-risk patients rather than those in the adjuvant setting for early-stage disease alone (T1/T2N0). Moreover, testing might be more appropriate in a neoadjuvant setting using pathological complete response as an end point to help select patients who would benefit from further therapy.

**Novel Agents in Bladder Cancer**

Cytotoxic chemotherapy remains at the core of systemic therapy options for bladder cancer, and no biological or immunotherapeutic agents are currently approved. An urgent, unmet need exists to develop and utilize novel therapies to improve outcomes in bladder cancer.

**Targeted Therapeutic Agents**

Many novel targeted therapies have been studied in bladder cancer with promising activity in early-phase trials. HER2/neu is variably expressed in primary tumors and metastases of urothelial bladder cancer, and it offers a rational target for drug discovery. In a phase II study, trastuzumab, a monoclonal antibody against HER2/neu receptor, was combined with a PGC regimen in HER2/neu-positive advanced urothelial carcinoma. The overall response rate was 70% and the median survival was 14.1 months, but more than 90% of patients had grades 3 to 4 myelosuppression, with 2 (5%) therapy-related deaths and more than...
20% patients with grades 1 to 3 cardiotoxicity. Epidermal growth factor receptor is overexpressed in more than 50% of bladder cancers and may be a prognostic marker.88 However, the tyrosine kinase inhibitor (TKI) gefitinib was not effective as a single agent and did not add to the efficacy of GC.89,90 Targeting the vascular endothelial growth factor (VEGF) axis is an appealing pathway in bladder cancer, and many trials using bevacizumab in bladder cancer are underway. Sunitinib, a VEGF TKI, was studied in previously treated patients with urothelial cancer and, although responses were seen in 4 of 77 patients, tumor regression or stable disease was seen in 43% of patients.91 Ongoing trials are evaluating its role alone or in combination in the first-line metastatic setting as well as the neoadjuvant and adjuvant settings. Pazopanib, another VEGF TKI, is also being evaluated in patients with metastatic urothelial cancer who are progressing on first-line chemotherapy. Fibroblast growth factor receptor 3 (FGFR-3) also plays a role in the oncogenesis of bladder cancer and represents a therapeutic target.92 Dovitinib is an oral inhibitor of VEGFR and FGFR and is being evaluated in combination with GC or carboplatin in bladder cancer (NCT01496534).

Immunotherapeutic Agents

Bacille Calmette-Guérin immunotherapy has been the standard of care for high-grade noninvasive urothelial carcinoma for a number of decades and there may be a potential role of immunotherapeutic agents for advanced bladder cancer.93 Many different immunotherapeutic strategies, including tumor-derived peptide vaccines, autologous T-cell vaccines, and viral vectors carrying gene encoding for tumor antigens, have been explored in early-phase studies in bladder cancer with variable results.94-100 ALT-801 (Altor Bioscience Corp, Miramar, FL), a human interleukin-2, single-chain, T-cell receptor fusion protein, is a targeted immunotherapeutic and is being studied in advanced bladder cancer in combination with GC, and early responses have already been observed.94 Active immunotherapy can potentially induce antitumor responses and is relatively well tolerated. However, larger phase II and III studies are needed to determine the clinical efficacy of various immunotherapy approaches, including testing them in combination with cytotoxic chemotherapy.

Conclusions

Bladder cancer is a chemosensitive disease, and systemic chemotherapy plays a role in its management. Cisplatin-based combination chemotherapy prolongs survival in the metastatic setting, and methotrexate, vinblastine, doxorubicin, and cisplatin or combination gemcitabine/cisplatin is the current standard of care. However, long-term survival in patients with metastatic disease is rare, and treatment is still palliative in nature. Combination chemotherapy that is not platinum based is recommended for patients who are ineligible for cisplatin therapy. Although carboplatin should not be substituted for cisplatin in fit patients, it may be considered in those who are ineligible for cisplatin. No approved second-line chemotherapy for metastatic bladder cancer exists, and response rates with available agents are variable.

The role of neoadjuvant cisplatin-based combination chemotherapy has been extensively evaluated and is associated with a modest but significant survival benefit. However, this is more pronounced in patients with high-risk disease, and a strong need exists to utilize this therapy. Studies with molecular markers and novel agents are needed to further improve outcomes in this setting and offer tailored therapy to patients based on risk stratification according to tumor type. The achievement of pathological complete response (pT0) with neoadjuvant chemotherapy has strong prognostic significance and may represent an alternate clinical end point for clinical trials. Although robust data are lacking for the use of chemotherapy in the adjuvant setting after cystectomy, it may be considered in patients who are at high risk for relapse. Unlike other solid tumors, targeted therapy is not well established in bladder cancer, and a critical need exists to develop novel agents that complement or are an alternative to conventional chemotherapies.

References


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