Neo-adjuvant chemotherapy for muscle-invasive bladder cancer: a look ahead

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Randomized clinical trials of neo-adjuvant cisplatin-based combination chemotherapy for locally advanced muscle invasive bladder cancer has shown a survival benefit over cystectomy alone. Pathologic complete response (pT0) after neo-adjuvant chemotherapy is emerging as a potentially important surrogate clinical end point. Future clinical trials incorporating targeted therapies with novel clinical end points may accelerate development of therapeutic strategies for locally advanced muscle invasive bladder cancer. Furthermore, evaluation of molecular markers may further help to stratify patients to a risk adapted approach.

Key words: bladder cancer, chemotherapy, neoadjuvant, pT0

introduction

Bladder cancer is a major health care problem in the United States. Approximately 63,210 new cases are estimated in 2005, with 13,180 deaths [1]. Bladder cancer represents 6% of all new cancer cases [2]. Bladder cancer is more common in men than woman and its incidence increases with age, with the median age at diagnosis being 65 years [3]. Bladder cancer may develop along a continuum of preneoplastic and preinvasive disease. Clinically, bladder cancer may be categorized as superficial, muscle-invasive or metastatic disease [3]. At presentation, approximately 75% of patients are diagnosed with superficial disease. Transitional cell carcinoma (TCC) is the most common histologic subtype accounting for approximately 95% of the cases [2]. Superficial bladder cancer is curable in most cases with transurethral resection and intravesical therapy. Radical cystectomy remains the standard for organ confined muscle-invasive disease. However, about 50% of patients will progress to metastatic disease and untreated patients die within 2 years [2]. Stage correlates closely with survival, with the 5-year survival for patients with superficial disease being 95%, as opposed to 50% with muscle-invasive disease and 6% for metastatic disease [4]. Due to advances in chemotherapy, patients with metastatic disease now have a median survival of about 1 year [5]. Nevertheless death from advanced disease ultimately occurs in more than 90% of such cases. Transitional cell carcinoma of the bladder is considered a chemosensitive tumor, as evidenced by a number of single agents that demonstrate objective response rates [6]. New combination regimens are currently been explored to further improve response rates, increase median survival and decrease toxicity. Hence, there is a continuous need to find the activity of newer and novel agents with unique mechanisms of action.

chemotherapy for metastatic disease

Chemotherapy is the mainstay of therapy for unresectable locally advanced or metastatic transitional cell carcinoma of the bladder. The majority of patients with advanced disease receive combination chemotherapy, usually with a platinum-based regimen. Before the development of effective chemotherapy, median survival rarely exceeded 3–6 months. With combination chemotherapy median survival of 1 year can now be achieved [5]. Interest in intensive systemic chemotherapy was stimulated by the results seen with a regimen of methotrexate, vinblastine, doxorubicin and cisplatin (MVAC) developed in 1983 at the Memorial Sloan-Kettering Cancer Center [7]. In a phase III trial, Logothetis et al. [8] compared MVAC with the CISCA regimen (cisplatin, cyclophosphamide and doxorubicin) and showed superior survival with the MVAC regimen. In another randomized trial, Loehrer et al. [9] compared single agent cisplatin with MVAC. Despite an improved median survival with MVAC (13 versus 6 months), the 6-year survival of MVAC was less than 4%. Using a logistic regression model the investigators reported for the first time that performance status is the most important prognostic factor with respect to response and survival. Although effective, this multidrug regimen was associated with problematic toxicities in some patients, particularly in the elderly or those with significant comorbidities [10]. Significant cardiac, renal and hematologic toxicity, with rates of neutropenic sepsis approaching 10%, has been seen in MVAC-treated patients. Over the past few years clinical research has focused on the development of new agents active in transitional cell carcinoma of bladder, with an improved toxicity.
profile. Several newer agents have been shown to have activity in advanced bladder cancer, including gemcitabine and the taxanes (Tables 1 and 2).

The activity of these novel chemotherapeutic agents, coupled with the inadequate survival resulting from single agents, led to a search for multidrug combinations to increase response rates and survival in advanced bladder cancer (Table 3). Von der Maase et al. [22] reported a randomized phase III trial showing that the combination of gemcitabine and cisplatin (GC) conferred a similar survival advantage to methotrexate, vinblastine, Adriamycin and cisplatin (MVAC) in the metastatic setting, with a better safety profile and tolerability. A recent update to this trial confirmed the long-term survival equivalence seen with GC versus MVAC [23]. The median PFS for GC versus MVAC was 7.7 versus 8.3 months, respectively. Median overall survival was similar as well at 14.0 versus 15.2 months, respectively (HR = 1.09, 95% CI 0.88–1.34, P = 0.66).

Of significance, treatment with GC provided comparable long-term survival versus MVAC as well (5 year-OS 13.0% versus 15.3%, respectively, P = 0.53). In terms of toxicity, neutropenic fever (2% versus 14%), neutropenic sepsis (1% versus 12%), grade 3/4 mucositis (1% versus 12%), alopecia (11% versus 55%) and toxic deaths (1% versus 3%) favored the GC arm versus MVAC arm, respectively.

Sternberg et al. [24] reported another randomized phase III trial comparing dose-dense MVAC with colony stimulating factor support versus standard MVAC chemotherapy. While there was no statistically significant difference in overall survival between the two arms (P = 0.122), dose-dense MVAC was associated with a significant improvement in overall response rates, complete response rates and progression-free survival. More recently, a randomized trial comparing the combination of docetaxel and cisplatin with standard MVAC with GCSF support was reported [25]. Median time to progression (9.4 versus 6.1 months, P = 0.003) and median overall survival (14.2 versus 9.3 months, P = 0.026) favored the MVAC arm. Furthermore, toxicity with MVAC chemotherapy was lower considerably with GCSF support. However, known prognostic variables were not used for stratification of patients in this study. This led to an imbalance in prognostic factors favoring the MVAC arm. Karnofsky performance status and visceral metastases have independent prognostic significance for long-term survival in unresectable or metastatic bladder cancer. Bajorin et al. [26] have reported that median survival times for patients with zero (KPS > 80% and absence of visceral metastases), one (KPS < 80% or presence of visceral metastases) or two risk factors (KPS <80% and presence of visceral metastases) had median survival times of 33, 13.4 and 9.3 months, respectively.

Recent trials have placed an emphasis on defining the nature of response and toxicities while recognizing that quality of life is an important end point in the treatment of patients with metastatic bladder cancer. Thus the development of less toxic, more active regimens is crucial to improving both survival and quality of life in these patients. Despite recent advances in the treatment of this disease there continues to be a need to identify new active agents and their toxicity spectra.

### neo-adjuvant chemotherapy for localized, muscle-invasive disease rationale

The biological basis for neo-adjuvant therapy rests on several factors [27, 28]. First, is the belief that cytotoxic chemotherapy is more effective when delivered to a small, well vascularized tumor. Secondly, because most agents are proliferation-dependent, the higher proliferation index of a small tumor renders it more susceptible to chemotherapy. Finally, as tumor cell numbers increase logarithmically, they acquire multiple additional mutations, some of which confer increased resistance to therapy over time [29].

The advantages of neo-adjuvant chemotherapy over an adjuvant design include: (1) better tolerance of chemotherapy prior to cystectomy than post-operatively; (2) avoidance of delay in administering chemotherapy due to post-operative morbidity and recuperation often encountered in the adjuvant approach; (3) urinary diversion after radical cystectomy may be associated with some decrement in renal function, thus limiting the use of adjuvant cisplatin, one of the most active agents in bladder cancer. Furthermore, neo-adjuvant chemotherapy allows individual assessment of in vivo tumor response, which can be a guide to future chemotherapy agent selection. Also, downstaging allows for better resectability, and in some selected patients, bladder conservation [30]. The main disadvantage of neo-adjuvant chemotherapy is that definitive local therapy (cystectomy or radiotherapy) is delayed during the treatment period. Furthermore, significant toxicity associated with neo-adjuvant chemotherapy may preclude potentially curative definitive local therapy. In addition, given that neo-adjuvant therapy relies on clinical (rather than pathologic) staging, some low-stage, low-risk patients may unnecessarily receive...
chemotherapy. In fact, a pilot study comparing clinical and pathologic staging in bladder cancer has demonstrated clinical staging errors prior to cystectomy in 38% of patients [31].

**impact on survival: randomized trials**

Numerous non-randomized clinical trials of neo-adjuvant chemotherapy followed by definitive local therapy (cystectomy or radiation therapy) have been reported in the literature. It can be concluded the chemotherapy given prior to definitive local therapy can be safely administered and is capable of producing pathologic complete responses (pT0) in about 25%–40% of patients [32] (Figure 1). Several randomized neo-adjuvant clinical trials have been reported to date (Table 4). Randomized trials with single agent cisplatin have been done followed by definitive local therapy with either surgery or radiation therapy [33, 34]. No survival advantage was seen with neo-adjuvant therapy in these trials. Although cisplatin is an effective drug in bladder cancer, monotherapy has been shown to be inferior to multiagent chemotherapy [9]. Furthermore, the small sample size and administration of only two doses of single agent cisplatin raises concerns about trial design. In one of these trials reported by Martinez-Pinero [34] with single agent cisplatin chemotherapy, 19.6% of patients achieved pT0 (no evidence of tumor in the cystectomy specimen). In another trial, neo-adjuvant single agent cisplatin chemotherapy for three treatment cycles was followed by concurrent cisplatin with radiation therapy or radical cystectomy. However, no survival advantage was found [35].

Subsequently, cisplatin doublets were investigated in the neo-adjuvant setting. In the Nordic-I trial, 325 patients were randomized to preoperative cisplatin plus doxorubicin for two cycles followed by local therapy versus local therapy alone [36]. Local therapy in this study consisted of preoperative RT to 20 Gy followed by cystectomy. In the initial report with a follow-up of 18 months, chemotherapy appeared to produce a 10%–15% improvement in survival (P = 0.034). However, the follow-up report demonstrated 5-year survival rates of 59% versus 51% (P = 0.1) in the chemotherapy and control arms, respectively. While no difference was observed for stage T1 and T2 disease, there was a 15% absolute improvement in overall survival with chemotherapy for patients with T3–T4a disease (P = 0.03). Cisplatin was then combined with methotrexate in two randomized trials of neo-adjuvant chemotherapy followed by definitive local therapy. The Nordic-II trial reported by Sherif et al. [37] compared three cycles of cisplatin and methotrexate followed by radical cystectomy versus cystectomy alone in 317 patients with T2–T4a, N0, M0 bladder cancer. The proportion of patients achieving a pT0 was 26.4% in the chemotherapy arm and 11.5% in the control arm (P = 0.001). However, despite substantial downstaging, no statistically significant survival benefit was seen with neo-adjuvant chemotherapy (53% versus 46% 5 year-OS for neo-adjuvant and control groups, respectively). In a prospective randomized trial by Sengelov et al. [38] (Daveca 89–02), 153 patients were randomized to preoperative cisplatin and methotrexate (CM) with folinic acid rescue versus no chemotherapy, followed by local therapy (radiation therapy or cystectomy). The addition of neo-adjuvant CM did not improve disease-free or overall survival in this population.

In recent years, modern multiagent chemotherapy has been evaluated before definitive local therapy for locally advanced bladder cancer in larger scale trials. Neo-adjuvant cisplatin,

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Regimen</th>
<th>RR</th>
<th>OS (months)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loehrer, 1992</td>
<td>269</td>
<td>Cisplatin versus MVAC</td>
<td>12%</td>
<td>8.2</td>
<td>Established superiority of multi-agent platinum regimen over single-agent platinum</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>39%</td>
<td>12.5</td>
<td>P = 0.0001</td>
</tr>
<tr>
<td>Logothetis, 1990</td>
<td>110</td>
<td>Cisca versus MVAC</td>
<td>46%</td>
<td>8.4</td>
<td>MVAC emerges as the superior multi-agent regimen</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>65%</td>
<td>11.1</td>
<td>P = 0.0003</td>
</tr>
<tr>
<td>MRC, 1998</td>
<td>214</td>
<td>MV versus CMV</td>
<td>19%</td>
<td>4.5</td>
<td>Established the importance of cisplatin in multi-agent chemotherapy regimens</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>46%</td>
<td>7</td>
<td>P = 0.0065</td>
</tr>
<tr>
<td>Maase, 2005</td>
<td>405</td>
<td>MVAC versus GC</td>
<td>46%</td>
<td>15.2</td>
<td>GC with better safety profile and tolerability</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>49%</td>
<td>14.0</td>
<td>P = NS</td>
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<tr>
<td>Sternberg, 2005</td>
<td>263</td>
<td>MVAC versus ddMVAC</td>
<td>58%</td>
<td>15.1</td>
<td>dd MVAC-improved PFS, reduced toxicity and dose delays</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>72%</td>
<td>14.9</td>
<td>P = 0.0417</td>
</tr>
<tr>
<td>Bamias, 2004</td>
<td>220</td>
<td>MVAC versus DC</td>
<td>54%</td>
<td>14.2</td>
<td>MVAC-GSCF, superior to DC trial did not stratify for known prognostic factors</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>37%</td>
<td>9.3</td>
<td>P = 0.026</td>
</tr>
<tr>
<td>Dreicer, 2004</td>
<td>85</td>
<td>MVAC versus CaP</td>
<td>36%</td>
<td>15.4</td>
<td>Closed early due to slow accrual</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>28%</td>
<td>13.8</td>
<td>P = NS</td>
</tr>
</tbody>
</table>

MVAC, methotrexate–vinblastine–doxorubicin–cisplatin; Cisca, cyclophosphamide–doxorubicin–cisplatin; MV, methotrexate–vinblastine; CMV, methotrexate–vinblastine–cisplatin; ddMVAC, dose-dense MVAC; DC, docetaxel–cisplatin; CaP, carboplatin–paclitaxel; NS, not significant; PS, performance status.
methotrexate and vinblastine (CMV) was studied in a bladder preservation trial conducted by the Radiation Therapy Oncology Group (RTOG) [39]. Here, 123 patients were randomized to two cycles of induction CMV followed by pelvic radiotherapy and concurrent cisplatin for two cycles given 2 weeks apart versus pelvic irradiation with concurrent cisplatin. No significant difference was seen between the neo-adjuvant chemotherapy and control arms in terms of local recurrence (9.8% versus 14.5%, respectively) or 5-year survival (48% versus 49%, respectively). The trial was closed prematurely as the neo-adjuvant arm had an unacceptable rate of severe complications.

The Medical Research Council and European organization for the Research and Treatment of Cancer (MRC/EORTC) reported results of the largest randomized trial of neo-adjuvant chemotherapy for TCC bladder to date [40]. This trial randomized 976 patients with T2–4a, N0, Mx disease to either local therapy alone, or three cycles of CMV chemotherapy followed by local therapy. The treating physician was permitted to determine local therapy, which consisted of either radiation or cystectomy for the majority of patients. Neo-adjuvant chemotherapy was found to improve the pT0 status of patients (32.5% versus 12% in the control arm). Initial analysis revealed a 15% reduction in risk of death with neo-adjuvant therapy, which translated into a 3-year survival difference of 5.5%, with 50% survival seen in the control arm, versus 55.5% survival in the chemotherapy arm. However, this possible survival benefit did not reach statistical significance (HR = 0.85, 95% CI 0.71–1.02, \( P = 0.075 \)). In 2002, long-term results of this trial were presented at ASCO, after a median follow-up of 7.4 years [41]. The updated results reported a similar magnitude of risk reduction with chemotherapy, although with greater statistical significance (HR = 0.85, 95% CI 0.72–1.00, \( P = 0.088 \)). Overall survival estimates for the treatment and control arms were 50% versus 44% at 5 years, and 43% versus 37% at 7 years, respectively, indicating an absolute survival improvement with chemotherapy in the range of 6%. The 3-year disease-free survival was significantly longer with neo-adjuvant chemotherapy (46% versus 39%, \( P = 0.019 \)).

In looking to reduce the toxicity of neo-adjuvant CMV, Abol-Enein et al. [42] examined the efficacy of CaMV, utilizing a carboplatin substitution for cisplatin. This study, reported in abstract form only, randomized 196 patients with T2 disease to CaMV for two cycles versus no preoperative therapy, followed by cystectomy. Neo-adjuvant chemotherapy was associated with a significantly greater proportion of patients alive and disease-free at 5 years (62% versus 42%, \( P = 0.013 \)). Mature data, including OS results, will be necessary in order to determine the true efficacy of this approach.

The benefit of neo-adjuvant chemotherapy was further supported by the largest US trial of neo-adjuvant chemotherapy prior to cystectomy, conducted by the Southwest Oncology Group (SWOG). Grossman et al. [43] reported on 317 patients over an 11-year period randomized to undergo cystectomy alone, versus three cycles of MVAC followed by surgery. Eligible patients had stage T2–T4, N0, M0 disease, and 60% had T3 or T4 disease. Patients were accrued over an 11-year period. Median survival in the surgery arm was 46 months versus 77 months in the chemotherapy arm (\( P = 0.06 \) by a two-sided stratified log-rank test). The 5-year survival for patients who underwent only cystectomy was 43% versus 57% for those who received neo-adjuvant MVAC (\( P = 0.06 \)). Although this result just failed to reach statistical significance when assessed by the widely accepted two-sided \( t \)-test, the survival difference was statistically significant when assessed using the one-sided \( t \)-test specified in the trial.

The neo-adjuvant chemotherapy group displayed a significantly higher proportion of patients with no residual disease compared with the cystectomy-alone group (38% versus 15%, \( P < 0.001 \)). Among the 38% (48 patients) who achieved a pT0 status in the combination-therapy arm, 26 patients initially had stage T2 disease and 22 patients had stage T3 or T4a disease. In both groups, improved survival was associated with the absence of residual disease in the cystectomy specimen. Among those patients achieving a pT0, the 5-year OS for

![Figure 1](image-url)

Figure 1. (A), Pre-tx. Hematoxylin and eosin stain of a bladder biopsy demonstrating irregular nests of neoplastic urothelial cells infiltrating through the submucosa and smooth muscle of the bladder, with accompanying inflammatory infiltrate. (H&E 40x). (B), Post-tx. Hematoxylin and eosin stain of a bladder biopsy demonstrating multinucleated giant cells, chronic inflammation and fibrosis, with no evidence of residual urothelial cell carcinoma after neoadjuvant chemotherapy. (H&E 100x).
chemotherapy and surgery arms was 85% and 82%, respectively. Conversely, 5-year OS for patients with residual disease at cystectomy was approximately 40%–45%. Therefore, the survival benefit of neo-adjuvant chemotherapy was strongly associated with downstaging of the tumor to pT0. MVAC chemotherapy did not adversely affect the patient’s chance of undergoing radical cystectomy, nor did it increase the risk of death or complications related to surgery.

**impact on survival: meta-analyses**

Several meta-analyses have been conducted in an effort to formulate definitive conclusions concerning neo-adjuvant therapy in bladder cancer. An initial meta-analysis reported by the Advanced Bladder Cancer (ABC) Meta-analysis Collaboration analyzed 2688 patients from 10 randomized trials of neo-adjuvant chemotherapy [44]. Overall mortality data was available and amenable to pooling from nine trials (2492 patients). An overall pooled HR of 0.91 (95% CI 0.83–1.01) was reported among the nine trials, translating into a 9% reduction in the risk of death and an absolute improvement in survival of 3% (48% versus 45%) with neo-adjuvant chemotherapy at 5 years that was statistically non-significant (P = 0.084). However, upon excluding the three trials utilizing single-agent cisplatin (no longer considered for routine use in clinical practice), a greater benefit was seen. The pooled HR for the six trials of combination chemotherapy showed a statistically significant 13% reduction in the risk of death, compared with local therapy alone (HR = 0.87, 95% CI 0.78–0.97, P = 0.016), equivalent to an absolute survival improvement of 5% (50% versus 45%) at 5 years. Combination chemotherapy was also associated with an improvement in disease-free survival (P = 0.0001), locoregional disease-free survival (P = 0.012) and metastasis-free survival (P = 0.001). A more recent meta-analysis was initiated by Cancer Care Ontario, identifying 11 randomized trials, comprising 2605 patients receiving platinum-based neo-adjuvant chemotherapy [44]. Notably, the aforementioned SWOG/Intergroup study results were available for inclusion in this analysis. When the eight trials that used cisplatin-based combination chemotherapy were examined, the pooled HR was 0.87 (95% CI 0.78–0.96). This hazard ratio was consistent with an absolute survival benefit of 6.5% (95% CI 2% to 11%) from 50% to 56.5%. Complete pathologic response (pT0) was observed in 14%–38.1% of patients in these trials. Overall, the rate of chemotherapy-related mortality was 1.1%. As in the previous meta-analysis, neo-adjuvant cisplatin monotherapy was not associated with a survival benefit versus local therapy alone. Therefore this meta-analysis, which included the SWOG Intergroup study results, confirmed the survival benefit associated with neo-adjuvant platinum-based combination chemotherapy in bladder cancer.
A recently published update to the Advanced Bladder Cancer (ABC) Meta-analysis Collaboration reported on 3005 patients from 11 randomized trials of neo-adjuvant chemotherapy in invasive bladder cancer [46]. Once again, a significant survival benefit was associated with platinum-based combination chemotherapy (HR = 0.86, 95% CI 0.77–0.95, P = 0.003). This equated to an absolute improvement in overall survival of 3% at 5 years. There was also a disease-free survival benefit associated with platinum-based combination chemotherapy (HR = 0.78, 95% CI 0.71–0.86, P < 0.0001). These findings confirm the strength and durability of the overall and disease-free survival benefit associated with neo-adjuvant chemotherapy in invasive bladder cancer.

### impact on bladder preservation

Neo-adjuvant chemotherapy also provides an opportunity to consider bladder preservation in select patients who achieve a pathologic complete response. The MSKCC has reported on their experience with neo-adjuvant MVAC followed by bladder-sparing surgery for patients with muscle-invasive T2–T3, N0, M0 bladder cancer [30]. Of 111 patients undergoing neo-adjuvant chemotherapy followed by transurethral resection (TUR), 60 (54%) achieved a complete pathologic response (pT0). Of these 60 patients, 43 underwent bladder-sparing surgery (either TUR or partial cystectomy). After a median follow-up of 10 years, 74% of these patients are alive, with only 30% of patients developing an invasive recurrence. This study suggests that a pT0 afforded by neo-adjuvant chemotherapy may safely permit bladder-preserving surgery in select patients.

### pathologic complete response: a new surrogate clinical end point?

One major advantage of the neo-adjuvant approach is the ability to assess the response of the primary lesion, which is of valuable prognostic significance. This concept was illustrated in a retrospective analysis of 75 patients receiving neo-adjuvant chemotherapy, followed by cystectomy for invasive TCC of the bladder [47]. A pathologic response (defined as pCR + pPR) was achieved in 57% of patients; 5-year overall survival in this group was 74%. Conversely, among those ‘non-responding’ patients (pNR) only 44% were alive at 5 years (P = 0.0021). Taking this concept a step further, a complete pathologic response to neo-adjuvant chemotherapy (pT0) is an end point more frequently assessed in recent clinical trials of neo-adjuvant therapy (Table 5). It has been hypothesized that attainment of a pT0 may have powerful prognostic significance, and in fact may represent a surrogate marker for overall survival.

Pathologic complete response rates are related to the stage and size of the primary tumor. Pathologic complete response rates have been reported in eight trials to date (Table 5). Cisplatin-based combination neo-adjuvant therapy has yielded pT0 rates of 14%–38.1% in various trials. A trial of single-agent cisplatin reported a pT0 rate of 17.8%.

Interestingly, it has been demonstrated that initial clinical ‘T’ stage was closely correlated with the ultimate attainment of a pathologic complete response after chemotherapy. Schultz et al. [48] assessed 111 patients receiving neo-adjuvant MVAC chemotherapy and stratified their pathologic response based on initial clinical T stage. Initial “T” staging of T2/T3A and T3b/T4 tumors yielded pT0 response rates of 43% and 9%, respectively. Therefore, the baseline patient population, and extent of their disease, must be considered when interpreting pT0 response rates across various clinical trials.

The prognostic significance of achieving pT0 status was highlighted in the recent meta-analysis from Winquist et al. [45]. Multiple patient, disease and treatment-specific factors have been assessed for prognostic significance in recent neo-adjuvant chemotherapy trials. Achievement of a pT0 has been found to be the only factor independently predictive of overall survival in multivariate analyses of four trials (comprising 786 patients) reporting on this end point. The recently reported US Intergroup study underscored this point, in showing much improved 5-year survival (85%) for the subgroup of patients deemed to be in pathologic complete remission at the time of definitive surgery.

Support for our proposal of a pT0 as a clinically important end point can be summarized by a review of Prentice’s criteria for surrogacy. Prentice developed operational criteria to assess the validity of a proposed surrogate clinical end point [49]. In order to suggest a pT0 at cystectomy as a surrogate clinical end point for neo-adjuvant chemotherapy (NC) for bladder cancer, we would have to demonstrate the following: (1) NC must have a significant effect on OS; (2) NC must have a significant effect on the incidence of pT0; (3) there must be

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. of patients</th>
<th>Chemotherapy regimen</th>
<th>pT0</th>
<th>Survival (pT0 versus residual disease)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRC/EORTC [29]</td>
<td>976</td>
<td>CMV × 3</td>
<td>32.5%</td>
<td>NR</td>
</tr>
<tr>
<td>CUETO [33], Spain</td>
<td>122</td>
<td>Cisplatin × 3</td>
<td>17.8%</td>
<td>73% versus 27% at 6.5 years</td>
</tr>
<tr>
<td>Abol-Enein et al. [41], Egypt (abstract)</td>
<td>196</td>
<td>Cisplatin × 2</td>
<td>14%</td>
<td>NR</td>
</tr>
<tr>
<td>Intergroup 0080 [42]</td>
<td>317</td>
<td>MVAC × 3</td>
<td>38%</td>
<td>85% versus 45% at 5 years</td>
</tr>
<tr>
<td>Millikan et al. [54], MDACC</td>
<td>63</td>
<td>MVAC × 2</td>
<td>40%</td>
<td>NR</td>
</tr>
<tr>
<td>GISTV [61], Italy</td>
<td>171</td>
<td>MVEC × 3</td>
<td>28%</td>
<td>NR</td>
</tr>
<tr>
<td>Cannibio et al. [62], Italy (abstract)</td>
<td>104</td>
<td>CF/RT × 2</td>
<td>27.5%</td>
<td>NR</td>
</tr>
<tr>
<td>Marcuello et al. [63], Spain (abstract)</td>
<td>66</td>
<td>CaMV × 3</td>
<td>20%</td>
<td>NR</td>
</tr>
<tr>
<td>Font et al. [64], Spain (abstract)</td>
<td>28</td>
<td>CMV × 3</td>
<td>27%</td>
<td>NR</td>
</tr>
</tbody>
</table>

a significant association between achievement of pT0 and OS; and (4) the full effect of NC on OS must be explained by achievement of pT0 status. The data reviewed in this paper certainly supports the fulfillment of criteria (1) and (2). Furthermore, based on the data from Grossman’s SWOG study, achievement of a pT0 was associated with improved survival, compared with those patients with residual disease at surgery, thus supporting criteria (3). The fourth criteria, perhaps the most difficult to prove, is also supported by the SWOG study. Specifically, for all patients who had a pT0 at cystectomy, the OS appeared to be independent of the initial treatment intervention; that is, 5-year OS for the chemotherapy and surgery arms was 85% and 82%, respectively, therefore, the achievement of pT0 following neo-adjuvant chemotherapy is worth consideration as a surrogate clinical end point and merits further study in clinical trial design.

**designing clinical trials utilizing pT0 as a primary end point**

Previous clinical trials of neo-adjuvant therapy in locally advanced bladder cancer have consistently utilized primary end points such as disease-free survival (DFS) and overall survival (OS) to evaluate efficacy of various treatment strategies. However, multiple studies have been plagued by logistical limitations, including inadequate patient sample size and limited patient follow-up. Perhaps the most illustrative example is that of the SWOG/Intergroup trial, which took 11 years to complete accrual. Ideally, important study questions in bladder cancer would not take this long to answer.

The recognition of pT0 as an end point, with its strong prognostic significance on patient outcome, provides a provocative basis for future trial design. As detailed above, multiple studies have now shown that complete pathologic response to preoperative therapy is a powerful surrogate of long-term disease-free survival in locally advanced bladder cancer. It can thus be hypothesized that a regimen that produces higher rates of pT0 in the neo-adjuvant setting may result in higher rates of long-term cure. Quantifying rates of pT0 at cystectomy (14%–40%, see Table 5), rather than patient events (such as relapse or death), should allow for smaller patient sample sizes necessary to adequately power prospective studies. Furthermore, since pathologic complete response data becomes available for analysis immediately after cystectomy, the efficacy of a treatment regimen is evident before long-term follow-up to determine survival. The pathologic complete response rate may thus function as a reliable, practical, surrogate end point that can potentially expedite the evaluation and development of novel therapeutic regimens in locally advanced, muscle-invasive bladder cancer. In addition, with pT0 status, we can shift the paradigm of neo-adjuvant bladder cancer chemotherapy to that of a risk-adapted or risk-stratified approach. Further adjuvant therapy may be studied in those patients with pathologic residual disease at time of surgery (which we know portends a higher risk of relapse/poorer prognosis).

We have put these principles to use in the design of a prospective, single-arm phase II trial evaluating the novel combination of cisplatin–gemcitabine–bevacizumab as neo-adjuvant therapy for localized, muscle-invasive bladder cancer (Figure 2). It should be noted, that while the MVAC regimen could certainly have been chosen as the ‘chemotherapy backbone’ in this trial, we chose cisplatin–gemcitabine based on the data (in the metastatic setting) suggesting equal efficacy with reduced toxicity [22]. The primary end point of this study, pT0 rate, will be analyzed at time of cystectomy, following four cycles of cisplatin–gemcitabine–bevacizumab therapy. For those patients with residual disease at the time of cystectomy, adjuvant therapy will be administered with three cycles of paclitaxel and bevacizumab. Taxanes are non-cross-resistant agents with demonstrated activity in bladder cancer and minimal renal clearance (which may be of benefit in this patient population that is often afflicted with postoperative urinary diversion). Continuation of bevacizumab out beyond chemotherapy completion in patients with residual disease is a concept that may be worth testing in future clinical trials. In addition, disease-free and overall survival will be evaluated, with the intention of confirming the powerful prognostic significance of a pathologic complete response. With newer generation chemotherapy agents and molecular targeted therapies on the horizon, improvement in pathologic complete response, and thus overall outcome, will be a primary goal for our bladder cancer patients.

**incorporating molecular markers in neo-adjuvant therapy**

The overall survival benefit attributable to neo-adjuvant chemotherapy has now been fairly well established. However,
there remains a substantial fraction of patients who do not respond to this preoperative chemotherapy, and are thus exposed to potential toxicities of treatment, without achieving significant clinical benefit. Equally important is the notion that delaying surgery may be particularly damaging to those patients who do not respond to preoperative therapy. Recent advances in our understanding of the molecular biology of transitional cell carcinoma-bladder may lead to the discovery of biologic markers able to predict tumor response to chemotherapy. Takata et al. [49] examined gene expression profiles of biopsy materials from 27 invasive bladder cancers prior to administration of preoperative MVAC. Utilizing a 27 648 gene cDNA microarray, investigators were able to identify 14 ‘predictive’ genes that were clearly expressed differently between responder and non-responder tumors. The authors postulated a numerical prediction scoring system that was able to accurately predict response to chemotherapy. Further study is certainly warranted to determine if indeed molecular analysis of bladder tumors can allow clinicians to ‘tailor’ decisions regarding neo-adjuvant therapy for bladder cancer based on likelihood of response.

Furthermore, molecular markers including p53 gene and angiogenesis factor expression have been studied as a means to select out poor prognosis patients. The majority of neo-adjuvant trials have included patients with T2–T4a disease. However, there is probably a subset of patients with organ-confined disease whose good prognosis would obviate the need and/or benefit of perioperative chemotherapy. The p53 tumor suppressor gene has been well characterized, with frequent observance in urothelial cancers. P53 mutation, as inferred through overexpression by IHC, is known to confer a worse prognosis in muscle-invasive bladder cancer. In one analysis of 243 patients undergoing radical cystectomy for pTa–pT4 TCC-bladder, nuclear p53 overexpression by IHC was significantly associated with an increased risk of disease recurrence (P < 0.001) and decreased overall survival (P < 0.001) [51]. Taking this concept a step further, Sarkis et al. [52] examined p53 mutation status in relation to neo-adjuvant chemotherapy for bladder cancer. In this report of 90 patients undergoing preoperative MVAC chemotherapy, patients with mutant p53 were three times more likely to die from their disease than those with wild-type p53. The impact of p53 overexpression on survival was predominantly in T2 and T3a tumors. These retrospective studies are now leading to prospective risk-directed trials using p53 status to determine therapy (i.e. whether to include perioperative chemotherapy) in patients with clinically favorable muscle-invasive tumors.

Inoue et al. [53] examined angiogenesis factor expression in 55 tumor samples of muscle-invasive TCC-bladder treated with neo-adjuvant MVAC. VEGF expression by in situ hybridization identified those patients at high risk of developing metastasis following aggressive local therapy. These findings, though provocative, will need to be confirmed in larger cohorts before ascertaining the true prognostic relevance of VEGF expression.

The prognostic significance of lymphovascular invasion (LVI) on pathology specimen has recently been emphasized. A retrospective analysis of 702 patients with invasive transitional cell carcinoma of the bladder was performed with focus on LVI and its effect on outcome [54]. The 10-year recurrence-free survival in patients without LVI was 74% compared with 42% in those with LVI (P < 0.0001). Similarly, 10-year overall survival was 43% in patients without LVI compared with 18% in those with LVI (P < 0.0001). Through Cox regression analysis, the authors concluded that pathologic stage and LVI status were independent prognostic variables for recurrence-free and overall survival.

By providing valuable prognostic information, the presence of LVI on pathologic specimen may help to guide therapy. Millikan et al. [55] conducted a phase III trial examining the timing of perioperative chemotherapy with respect to surgery in patients with high-risk resectable urothelial cancer. Here, 140 patients were randomized to receive either two cycles of neo-adjuvant MVAC followed by surgery plus three additional cycles of adjuvant MVAC versus initial cystectomy followed by five cycles of adjuvant chemotherapy. The accuracy of clinical versus pathologic staging was evaluated in this study, particularly in the arm receiving initial surgery. Of those patients with clinically organ-confined disease, 61% were upstaged on pathologic analysis. All of these tumors had LVI present on initial TURBx. Therefore, the presence of LVI may identify a group of apparent low-risk patients who carry the same poor prognosis as patients with clinically extravesical disease; perioperative chemotherapy may be recommended in this group.

An emerging molecular marker, perhaps of more immediate clinical significance from a therapeutic perspective, is the EGFR. The EGFR protein, a well characterized member of the tyrosine kinase receptor family, plays a role in signaling pathways that cause increased proliferation and cell survival [56]. Approximately 50% of bladder tumors demonstrate strong immunohistochemical staining for EGFR. Furthermore, overexpression of EGFR has been shown to be associated with muscle invasion and poorly differentiated histology [56]. In fact, Mellon et al. [57] prospectively assessed the EGFR status in 212 patients with newly diagnosed invasive bladder cancer, followed for a mean of 26.5 months. EGFR positivity was found to be an independent predictor of stage progression and overall survival. Gefitinib (small molecule tyrosine kinase inhibitor) has demonstrated potent in vitro inhibitor activity against a range of human bladder TCC cell lines [58]. Clinical trials of anti-EGFR agents, either alone or in combination with chemotherapy, are underway.

A related therapeutic target, somewhat further along in clinical investigation, is the HER2/neu protein. The documented frequency of erbB-2 overexpression in bladder tumors has been variable, although with rates as high as 46%–54%, and is correlated with high-grade and invasive specimens [58–60]. Preliminary data has demonstrated the feasibility and activity of trastuzumab in combination with chemotherapy for metastatic TCC of the bladder [59]. An ongoing randomized phase II study is looking at gemcitabine plus a platinum agent with or without trastuzumab in advanced or metastatic bladder cancers overexpressing HER2 [60].

According to the traditional model, once molecularly targeted agents demonstrate efficacy in the metastatic setting, they are then tested in earlier phases of the disease (i.e. neo-adjuvant therapy). Alternatively, if we are to accept pathologic response
as a valid marker of outcome, then one could consider incorporating novel agents initially into a neo-adjuvant trial design, as discussed previously.

conclusions

The role of neo-adjuvant chemotherapy has been extensively investigated in muscle-invasive bladder cancer. Although various individual prospective trials have failed to demonstrate an overall survival benefit, these studies have been plagued by either inadequate chemotherapy regimens or insufficient sample size. Recent large, prospective randomized trials, as well as three meta-analyses, provide ample support for a survival benefit associated with neo-adjuvant platinum-based combination chemotherapy prior to definitive local therapy for muscle-invasive bladder cancer. The magnitude of benefit seen (absolute OS advantage 6.5%) is similar to that seen for perioperative chemotherapy for other primary solid tumor malignancies, notably breast and colorectal. Further studies are required to identify the optimal neo-adjuvant regimen and to examine whether the addition of biological agents can increase efficacy and long-term outcomes. Neo-adjuvant strategies offer two principle advantages that may prove integral in advancing this field: (1) use of pT0 as a surrogate end point to facilitate and expedite evaluation of new agents/regimens; and (2) in vivo assessment of molecular markers that may offer valuable prognostic information for risk-stratified therapy. Therefore, the use of neo-adjuvant therapy in muscle-invasive bladder cancer may help us to refine further the answers to the two most valuable questions: Whom to treat? and What to treat with?

search strategy and selection criteria

Data for this review were identified by searches of MEDLINE, Current Contents, PubMed and references from relevant articles using the search terms 'neo-adjuvant chemotherapy' and 'bladder cancer'. Abstracts and reports from meetings were included only when related directly to, or supportive of, previously published work. Only papers published in English between 1980 and 2005 were included.

references