Published in final edited form as:
Urol Oncol. 2012 November ; 30(6): 772–780. doi:10.1016/j.urolonc.2012.01.012.

Practical Use of Perioperative Chemotherapy for Muscle-Invasive Bladder Cancer: Summary of Session at the Society of Urologic Oncology Annual Meeting

Andrea B. Apolo[1], **H. Barton Grossman**[2], **Dean Bajorin**[3], **Gary Steinberg**[4], and **Ashish M. Kamat**[2]

[1]Medical Oncology Branch, National Cancer Institute, Bethesda, Maryland [2]Department of Urology, University of Texas MD Anderson Cancer, Houston, TX [3]Genitourinary Oncology Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center [4]Section of Urology, University of Chicago Medical Center, Chicago, IL

Abstract

At the 11th annual meeting of the Society of Urologic Oncology, an expert panel was convened to discuss the practical use of perioperative chemotherapy for muscle-invasive bladder cancer. The discussion was structured as a case-based debate among the panelist. The topics included: neoadjuvant chemotherapy with a focus on T2 disease, pros and cons, survival data, tolerability of cisplatin-based therapy, can we avoid radical cystectomy in complete responders, limitations and alternatives to cisplatin-based therapy, management of 'suboptimal' chemotherapy, residual disease after neoadjuvant chemotherapy, adjuvant chemotherapy and key aspects of radical cystectomy and lymph-node dissection in multi-modal therapy. The presentations were derived from published literature. The panelists agreed that patients with muscle-invasive bladder cancer should be managed with a multidisciplinary team including urologist and medical oncologist. Cisplatin-based neoadjuvant chemotherapy has demonstrated improved survival and should be incorporated into the management of all eligible patients with muscle-invasive bladder cancer. However, in some centers neoadjuvant chemotherapy is reserved for patients with >T2 disease or high-risk features. There are no data for the administration of non-cisplatin based neoadjuvant chemotherapy such as carboplatin-combinations. Cisplatin-ineligible patients should proceed directly to surgical extirpation with adjuvant cisplatin-based chemotherapy considered based on pathologic findings. However, the data for adjuvant chemotherapy is less compelling. As our refinement of the selection process continues we may be able to better identify subsets of patients who may be spared chemotherapy, but much work remains to be done in this arena. The current standard for muscle-invasive bladder cancer patients is cisplatin-based neoadjuvant chemotherapy followed by radical cystectomy and pelvic lymph-node dissection.

Corresponding Author: Ashish M. Kamat, MD, Department of Urology, Unit 1373, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030, Telephone: 713-792-3250, Fax: 713-794-4824, akamat@mdanderson.org.

Keywords

Bladder Cancer; neoadjuvant chemotherapy; adjuvant chemotherapy; perioperative chemotherapy; muscle invasive bladder cancer

Introduction

Muscle-invasive bladder cancer (MIBC) is a potentially curable disease, yet too many patients die from recurrence after undergoing major extirpative surgery. Recent – and not so recent – advances have helped us understand that urothelial cancer requires a multidisciplinary approach with close integration between the surgeon and the medical oncologist to provide patients with the best therapy. However, peri-operative chemotherapy, whether it be neoadjuvant or adjuvant, is sorely underutilized by physicians treating this disease, despite a vocalized commitment on the part of the urologic community to follow current recommendations[1]. Reasons for this are varied but a common theme is sub-optimal understanding of the benefits of multimodal therapy among patients and providers.

At the 11th annual meeting of the Society of Urologic Oncology, an expert panel was convened to discuss the practical use of perioperative chemotherapy for MIBC. The experts – Drs. Apolo from the National Cancer Institute (NCI), Bajorin from Memorial Sloan Kettering Cancer Center (MSKCC), Grossman from M.D. Anderson Cancer Center (MDACC) and Steinberg from the University of Chicago (UC) – were charged by the moderator Dr. Kamat, from MDACC – with coming up with practical solutions to often discussed issues in this arena using a case-based approached. Cases were presented by the moderator representing treatment controversies followed by debates by the panel with pro and con positions assigned by the moderator. This article is a synopsis of the panel discussions addressing common controversies that exist regarding the use of peri-operative chemotherapy in MIBC. We focus the discussion on the incorporation of chemotherapy and surgery in the management of patients with MIBC. Radiation therapy was not included in the discussion even though it has a role in select situations.

Neoadjuvant Chemotherapy for Muscle Invasive Bladder Cancer with a focus on T2 tumors: Pros

Muscle-invasive bladder cancer is a systemic disease and the cause of relapse in patients undergoing radical cystectomy is often due to micrometastatic disease at the time of surgery. Therefore, it is important to administer systemic therapy early in the disease process to eradicate micrometastasis outside the surgical field. Neoadjuvant chemotherapy is historically easier to administer than adjuvant chemotherapy, and neoadjuvant therapy appears more beneficial. Phase III clinical trials of neoadjuvant cisplatin-based chemotherapy that have demonstrated a survival benefit have all been conducted in clinical T2-T4a disease[2–4]. If one analyzes just the T2 tumors, they do extremely well with neoadjuvant chemotherapy. The randomized Southwest Oncology Group (SWOG) 8710 trial in which neoadjuvant methotrexate, vinblastine, adriamycin (doxorubicin) and cisplatin (MVAC) followed by cystectomy compared to cystectomy alone demonstrated a 2.5 year survival advantage in patients with T2 disease (105 versus 75 months (P =0.05)). While some centers have advocated a stratifying approach to neoadjuvant chemotherapy by selecting patients with greater than T2 disease or other high risk features, there are some concerns about this approach. First, there is a high discrepancy between clinical staging and actual pathologic staging in MIBC. Recent studies examining this issue reported that 43–73% of patients having clinical T2 disease pre-cystectomy were upstaged on pathologic assessment[5–6]. Extravesical extension, spread to adjacent organs, or lymph-node

involvement at cystectomy for “organ-confined” disease has been well documented over the past two decades[7–10]. Microscopic lymph-node metastases are found in 16–22% of patients who undergo pelvic lymphadenectomy during radical cystoprostatectomy for clinically T2 tumors [11–13].

Post-chemotherapy staging is equally inaccurate since, despite improved imaging and aggressive post-chemotherapy transurethral staging biopsies, bladder tumors after chemotherapy are frequently understaged. A SWOG phase II study (S0219) of neoadjuvant paclitaxel, carboplatin and gemcitabine underscores this issue: Ten of the 34 patients who received neoadjuvant chemotherapy and achieved T0 status determined by CT scans and TURBT underwent an elective cystectomy of which 60% had residual muscle-invasive or node-positive disease [14]. These studies highlight clinical inaccuracies in staging patients with invasive bladder cancer, either before or after neoadjuvant chemotherapy. This reinforces the concept that the standard of care for MIBC, including T2 only disease should include neoadjuvant chemotherapy followed by definitive surgery consisting of a well performed radical cystectomy and thorough bilateral pelvic lymph-node dissection.

Neoadjuvant Chemotherapy for Muscle Invasive Bladder Cancer with a focus on T2 tumors: Con

Unfortunately, the evidence for the use of neoadjuvant chemotherapy in patients with T2 only disease, is not as clear-cut as presented above. If neoadjuvant chemotherapy was benign and highly successful, the paradigm for treating MIBC would change and surgery would become an occasional adjuvant to chemotherapy. However, contemporary chemotherapy for locally advanced bladder cancer is associated with a low cure fraction (despite high initial response rate). While it is true that the SWOG neoadjuvant MVAC (8710) study stratified enrollees by stage, T2 vs >T2[2], this study used an old staging system and T2 would currently be called T2a. In both low stage and high stage disease, neoadjuvant chemotherapy was associated with better survival. However, a greater difference in the survival curves was seen in the higher stage participants. This should not be surprising because more recurrences would be expected in this population. At MDACC, neoadjuvant chemotherapy is reserved for those who are more likely to fail with surgery alone. The criteria for the use of neoadjuvant chemotherapy are T3 disease or higher, lymphovascular invasion, hydronephrosis, and adverse histology. The belief is that limiting neoadjuvant therapy to high risk disease according to the MDACC criteria provides a reasonable balance between efficacy and toxicity. MDACC does not, however, condone up front radical cystectomy for all patients with MIBC.

Practical Points with Neoadjuvant Chemotherapy

Survival Data

The mature results of the Medical Research Council (MRC) and European Organization for the Treatment and Cure of Cancer (EORTC) trial of neoadjuvant cisplatin-based chemotherapy show an absolute survival benefit of 6% and a relative reduction in the risk of death resulting from bladder cancer of 16% at 10 years in 976 randomized patients with MIBC[4]. Some physicians feel that the difference in absolute survival between those that receive neoadjuvant chemotherapy and those that do not is “too small”, and that an improvement in survival of 10% is needed to justify the use of neoadjuvant cisplatin-based therapy in routine practice. A meta-analysis of over 3000 bladder cancer patients with MIBC who received cisplatin-based neoadjuvant chemotherapy also showed a survival benefit of “just” 6% and a 14% risk reduction in mortality at 5 years[15]. However, these data are quite similar to analyses for breast cancer and colon cancer peri-operative chemotherapy. A meta-analysis of 17,723 women with breast cancer showed a survival benefit of 7% and a 15%

decreased mortality at 10 years for women age 50 and under, leading to the establishment of adjuvant chemotherapy as the standard of care[16]. A pooled analysis of 3,302 patients with colon cancer showed a survival benefit of 7% at 5 years[17], also justifying this approach as the standard of care. Thus, the survival benefit for cisplatin-based neoadjuvant chemotherapy in MIBC is comparable to the absolute survival benefit seen with other cancers in which perioperative chemotherapy is the standard of care.

Tolerability of Cisplatin-based Neoadjuvant Chemotherapy and Effect on Radical Cystectomy

A close review of phase III data supports the notion that neoadjuvant chemotherapy can be incorporated into multi-modality therapy without adverse consequences. Patients treated with neoadjuvant cisplatin, methotrexate and vinblastine (CMV) had a favorable side effect profile[3–4] and serious adverse effects were not common. The mortality rate in patients assigned to chemotherapy was 1%, remarkable for a study conducted in over 100 centers in 20 countries. Drug delivery was excellent with only 20% of patients receiving less than the intended number of treatment cycles. In the SWOG phase III trial, the authors concluded that MVAC could be given safely before radical cystectomy. Overall the adverse effects were moderate and the chemotherapy side-effects self-limiting. There were no treatment-related deaths, MVAC did not adversely affect a patient's chance of undergoing radical cystectomy, and there were no increased surgical complications for the MVAC treated patients. This study showed that in a large multi-institutional study the rates and types of postoperative complications were low and equivalent in the two arms.

In another randomized study involving neoadjuvant MVAC patients were randomized to receive 2 cycles of neoadjuvant MVAC, cystectomy, and 3 cycles of adjuvant MVAC or cystectomy and 5 cycles of adjuvant MVAC [18]. In this study, the median time to regular diet and discharge was 1 day less in those receiving neoadjuvant chemotherapy. There were, however, more patients in the neoadjuvant arm that had postoperative ileus which can be a severe complication in older patients. The study arm did not affect the type of urinary diversion, with a greater proportion of patients in the neoadjuvant arm receiving orthotopic urinary diversions. Importantly, in the neoadjuvant arm only 1 of 63 patients had surgical positive margins, while 7 of 66 in the initial surgery arm had positive margins.

In the United States, gemcitabine and cisplatin (GC) is frequently used in the neoadjuvant setting instead of MVAC or CMV. When GC was compared to MVAC in a randomized phase III[19] trial for metastatic disease, GC had a better safety profile than MVAC. The rate of neutropenic fever, neutropenic sepsis and toxic deaths were 2%, 1% and 1%, respectively with a median of six cycles of GC. Four cycles of GC at 3-week intervals has been examined in the neoadjuvant setting with drug delivery exceeding 90%, attesting to the feasibility of this regimen. Achievement of pT0 status after chemotherapy for GC was comparable to MVAC[20–21]. Nevertheless, there is no level 1 evidence for the use of GC in the neoadjuvant setting and variable rates of pT0 have been reported[20–22]. Therefore, some providers prefer to use neoadjuvant MVAC instead of GC.

A randomized study in metastatic disease of standard MVAC vs. dose-dense MVAC (ddMVAC) showed that by eliminating day 15 and 22 of methotrexate and vinblastine the regimen could be completed faster, with less toxicity, and better outcome[23]. A randomized controlled study of ddMVAC versus ddGC in patients with inoperable or recurrent urothelial cancer was terminated early for poor accrual and lack of funding[24]. To salvage the study, a single-arm cohort of non-controlled patient receiving ddMVAC was added. Both regimens, ddMVAC and ddGC, were comparable in terms of overall survival and progression free survival, with a better toxicity profile in the ddGC group. Though, change in the study

design makes the results difficult to interpret. Important questions remain regarding the efficacy and relative toxicity of standard GC versus. ddMVAC.

Can we Avoid Radical Cystectomy in Patients who appear to have 'responded' to Neoadjuvant Chemotherapy?

The short answer is no. While the SWOG neoadjuvant MVAC study found that patients who were pT0 at cystectomy in both arms had an improved outcome participants were 2.5 times more likely to achieve pT0 status if they were randomized to the neoadjuvant chemotherapy arm[2]. The question then arose that while all of these patients received cystectomy and had good outcome, could similar results be achieved without surgery? Bladder sparing has been explored in patients who have received "neoadjuvant" chemotherapy. Three cycles of MVAC were administered to 104 patients with MIBC and additional treatment was based on restaging[25]. Partial cystectomy was performed in 13 patients and 52 had transurethral resection alone. Of the 37 patients that were cT0, a third (12) died (with either invasive recurrence, and/or metastatic recurrence). The outcome of 63 patients receiving 4 cycles of cisplatin-based chemotherapy who refused cystectomy because they achieved a clinical complete response has also been reported[26]. About a third (36%) of patients subsequently died of bladder cancer. The risk of death was high (75%) in patients experiencing recurrent invasive bladder cancer.

The question of what to do with patients who achieve a clinical complete response was evaluated in the SWOG phase II study (S0219)[14]. Of the 34 who achieved cT0, 10 had immediate cystectomy. Six of the ten (60%!) were found to have pT2–4, MIBC. Overall, the data shows that some patients will achieve cT0 disease after neoadjuvant chemotherapy and have durable disease free survival. However, a significant portion of patients who achieve cT0 will be understaged and have a high risk of dying of their disease. With the current state of our knowledge, choosing observation after achieving a cT0 state with neoadjuvant chemotherapy is akin to playing Russian roulette, and the panel does not recommend this approach.

Limitations and Alternatives to Cisplatin-based Chemotherapy

While we advocate the use of neoadjuvant cisplatin-based chemotherapy, we also recognize that there are several contraindications to the use of cisplatin chemotherapy, including hearing loss/dysfunction, cardiac dysfunction, poor performance status and renal insufficiency. A large proportion of patients with urothelial cancer have impaired renal function due to multiple factors, including medical comorbidities, age-related decline in glomerular filtration rate, and ureteral obstruction. The degree to which impaired renal function limits the widespread use of cisplatin in the peri-operative setting was explored in a series of over 500 patients who underwent a cystectomy without neoadjuvant chemotherapy at MSKCC [27]. The overall proportion of patients ineligible for cisplatin-based chemotherapy using the Cockroft-Gault equation was >40% of patients over 70 years of age.

An approach used in the management of patients with mild renal insufficiency is splitting the dose of cisplatin in GC from day 1 to day 1 and 8 of a 3 week cycle [28]. A widely used approach – which we do not recommend – for patients that are considered 'unfit' for cisplatin-based therapy is replacing cisplatin with carboplatin, despite the lack of any definitive data for benefit. Carboplatin-based therapy has not been satisfactorily compared with cisplatin-based therapy in phase III trials in patients with metastatic disease or MIBC. In fact, randomized phase II trials in advanced disease patients demonstrate that carboplatin therapy is inferior in terms of complete response and overall response[29–31]. The median survivals for carboplatin-treated patients in these studies are frequently less than one year

whereas the median survival for cisplatin-treated patients is typically 12–15 months suggesting that survival for patients with metastatic disease is compromised with carboplatin therapy. The SWOG phase II study (S0219) used carboplatin, gemcitabine and paclitaxel in the neoadjuvant setting and demonstrated a poor median survival and a very high rate of persistent cancer at cystectomy[14]. Based on these limited observations, patients with MIBC that are cisplatin-ineligible should proceed directly to cystectomy or be considered for a trimodality therapy bladder preservation approach. Substituting carboplatin for cisplatin in the peri-operative setting is not a standard of care and should be avoided given the lack of a survival benefit and the danger of delaying curative local therapy.

What To Do When Patients Receive 'Suboptimal' Neoadjuvant Chemotherapy?

The inability to give adequate chemotherapy is relative just as the the statement is true for surgery. A patient with a variety of comorbidities may receive less than optimal chemotherapy because of perceived risks, while another physician may be willing to treat such an individual aggressively with "adequate" chemotherapy. Of course, some patients have significant medical problems that will prevent them from safely receiving definitive chemotherapy. A second relevant concept is an understanding of the benefit of combined chemotherapy and surgery. Overall, for locally confined disease, high quality radical cystectomy offers a greater chance of long term survival than chemotherapy.

Patients who receive suboptimal neoadjuvant chemotherapy should be evaluated by a skilled medical oncologist. Should the neoadjuvant chemotherapy be indicated and there is reasonable probability that the patient will tolerate aggressive chemotherapy followed by cystectomy, then a second attempt at providing high quality neoadjuvant chemotherapy should be made. If there are sufficient comorbidities that additional neoadjuvant chemotherapy will not be tolerated, then radical cystectomy should be performed and adjuvant chemotherapy can be considered at a later date.

Management Of Residual Disease After Neoadjuvant Chemotherapy

As we have discussed, cisplatin-based neoadjuvant chemotherapy improves overall survival in patients with MIBC mainly by downstaging the muscle-invasive tumor (stage T2-T4a) to non-muscle invasive disease (<T2)[2, 18, 32–33]. In the SWOG phase III 8710 trial the likelihood of long term survival was >85% at 5 years in patients who achieved a pT0 status and <40% at 5 years in patients that had residual muscle-invasive disease, >pT2 at the time of cystectomy in both arms [2]. Patients who received neoadjuvant chemotherapy that achieved a pT0 appeared to also have a better outcome than those that had residual non-muscle invasive disease <pT2 (pTa, pT1 and carcinoma in situ), the difference however, did not achieve statistical significance[34]. In another randomized study of MIBC patients who received both neoadjuvant and adjuvant MVAC vs. only adjuvant MVAC, 40% of the patients that received neoadjuvant MVAC had < pT1 at cystectomy and only 12% experienced relapse. However, patients with pathologic involvement of the pelvic lymph-nodes despite neoadjuvant MVAC did poorly; 86% of these patients subsequently experienced relapse and died of metastatic cancer[18].

More patients with MIBC are downstaged to non-muscle invasive disease with cisplatin-based neoadjuvant chemotherapy than with a transuretheral resection alone. Published surgical series of patients with MIBC have demonstrated that the pT0 rate after transurethral resection with no prior chemotherapy ranges from 5–15% [2, 7, 13, 35–36] (see table 1), although in 'low-risk' populations it can be as high as 30.5%[6] .

Patients with no pathologic response to neoadjuvant chemotherapy have a poor prognosis. However there are no data demonstrating a survival benefit in giving additional adjuvant chemotherapy after 12 weeks of cisplatin-based neoadjuvant chemotherapy. A retrospective study of 37 patients with tumor in the lymph-nodes after preoperative chemotherapy reported an improvement in recurrence-free and disease-specific survival in patients that received a variety of different "adjuvant" chemotherapy regimens including non-platinum combinations[37]. This is an interesting and hypothesis generating result but we still do not have high level evidence to treat patients with residual disease after neoadjuvant chemotherapy with additional adjuvant chemotherapy. More than half of the patients in this retrospective report had clinical stage 4 disease prior to receiving any chemotherapy and are a different population than patients that are eligible for neoadjuvant chemotherapy with stage T2-T4a disease.

Now that more and more patients are appropriately being treated with neoadjuvant chemotherapy, we need to add to our limited experience with subsequent therapies at the time of relapse. An emerging trend in the treatment of patients with relapse disease in fist-line chemotherapy trials, is to allow for retreatment with the same or similar cisplatin-combination (GC, MVAC, ddMVAC) as long as the therapy was completed 6 months-1 year prior to the detection of relapse metastatic disease[38–41]. However, there is a great concern of cross-resistance among cisplatin-based regimes. There are no established standards for the treatment of patients with relapsed disease after peri-operative chemotherapy. New guidelines are needed to help in the management of this emerging patient population.

Adjuvant Chemotherapy

The data for adjuvant chemotherapy are less succinct, and this should not be used as a replacement for neoadjuvant chemotherapy. However, there are patients who benefit from adjuvant chemotherapy, including those thought to be candidates for up front radical cystectomy who end up having extensive disease. Unfortunately, patients with bladder cancer are usually elderly and tend to have multiple co-morbidities, therefore, delivering adjuvant chemotherapy to these patients after a radical cystectomy can be challenging. The impact of post-operative complications on the timing of adjuvant chemotherapy was described in 1142 consecutive patients undergoing a radical cystectomy[42]. In this report 30% of patients experience a grade 2–5 complication potentially interfering with the administration of chemotherapy.

The role of adjuvant chemotherapy in MIBC has been evaluated in a series of randomized studies. Six randomized trials of adjuvant chemotherapy[43–48] from1991 to 2001, were included in a meta-analysis published in 2005[49]. In the meta-analysis there was a suggestion of benefit with adjuvant cisplatin-based combination chemotherapy with a HR 0.75 but the trials were small and underpowered. The authors concluded that the power of the meta-analysis was limited and could not be used to guide the decision analysis with regard to adjuvant therapy.

At the American Society of Clinical Oncology (ASCO) annual meeting in 2008, preliminary results from an Italian multicenter phase III trial were presented[50]. Patients with high risk disease after cystectomy with either extranodal or nodal involvement were randomized to receive GC for 4 cycles or observation after surgery followed by GC at relapse. The study was designed to enroll 610 patients but unfortunately closed because of poor accrual after randomizing only 194 patients. In the adjuvant treatment arm only 62% of patients received all 4 courses of chemotherapy; not unexpected, given the previously reported rate of post-operative complications after cystectomy in this frail patient population[42]. At a median

follow-up of 27 months, there was no significant difference in disease-free survival (p=0.58).

At the ASCO annual meeting in 2009 SWOG presented preliminary results of an adjuvant chemotherapy trial where patients were randomized to receive adjuvant MVAC based on their tumor p53 status by immunohistochemistry. The patients randomized had organ-confined disease (pT1/T2N0M0), and were a more favorable group of patients with a lower than expected event rate based on prior adjuvant studies. Among the patients with p53 positive tumors who were randomized, there were no differences in time to recurrence or overall survival[51] . The trial was closed after the interim analysis based upon futility due to the lower than expected event rate and problems with patient acceptance for randomization, both of which compromised study power.

The Spanish Oncology Genitourinary Group (SOGUG) presented preliminary results of a randomized phase III trial comparing adjuvant paclitaxel, gemcitabine, and cisplatin (PGC) to observation in patients with high risk (T3/T4 or node positive) MIBC at the ASCO annual meeting in 2010[52], . The trial was designed to randomize 340 patients to either four cycles of PGC or to observation but was closed early because of poor accrual. A statistically significant increase in overall survival with adjuvant chemotherapy (five-year survival 60 versus 30 percent, HR 0.44) at a median follow-up of 51 months was reported. However, the results are difficult to interpret because of the poor accrual and early closure of the trial.

The European Organization for Research and Treatment of Cancer (EORTC) conducted a phase III trial of early versus delayed chemotherapy after cystectomy for patients with pT3-T4 or node positive disease. The study was designed to randomize 644 patients to one of three adjuvant chemotherapy regimens (MVAC, high dose MVAC, or GC) or observation. The study closed after enrolling 298 patients. Although this study did not meet its accrual goal and was terminated early, it is the largest randomized adjuvant trial to date and the results of this trial when available may provide important data as to the role of adjuvant chemotherapy in patients with MIBC.

Thus, despite the efforts of multiple cooperative groups and investigators, the evidence supporting adjuvant chemotherapy remains unclear. Meta-analyses need to be updated to include these large randomized trials and provide more information regarding the role of adjuvant chemotherapy in this patient population. Until then, the panel stated that there is insufficient evidence to support the routine use of adjuvant chemotherapy. All patients should be informed about the benefits of neoadjuvant chemotherapy. If the patient refuses or did not receive neoadjuvant chemotherapy and has perivesical tumor involvement or greater (>pT2) and/or local regional lymph-node involvement after cystectomy then adjuvant chemotherapy should be considered but the data are less compelling. Outside of a clinical trial, patients being considered for adjuvant chemotherapy should have good renal function in order to tolerate therapy with 3 or 4 cycles of a cisplatin-based combination.

Key Aspects of Radical Cystectomy and Lymph-node Dissection in Relation to Impact on Multi-Modal Therapy

Radical cystectomy and pelvic lymph-node dissection (PLND) are the standard of care for patients with MIBC. As mentioned earlier, if a patient without evidence of metastatic disease at presentation must choose between chemotherapy and surgery, or surgery alone, surgery offers the best chance of cure as a single modality therapy. However, this chance of cure is at best, 81% at 5 years as demonstrated in the MDACC ‘Low Risk’ population and at worst as low as 25% for patients with unrecognized nodal disease who are not candidates for

adjuvant chemotherapy post-surgery. Thus, a thorough surgery is a crucial step in the multi-modal management of patients with MIBC.

Patients treated with radical cystectomy and PLND typically achieve excellent local control of their disease. However, the patients that do have recurrence of their disease predominantly recur with distant metastases[13, 53–54]. Systemic chemotherapy is the primary form of treatment for patients with lymphatic or hematogenous metastases. Still, some patients initially diagnosed with lymph-node metastases who respond to chemotherapy (ideally treated for metastatic disease with 6 instead of 3–4 cycles of cisplatin-based therapy) with radiographic resolution of the metastases may benefit from consolidation surgery with a radical cystectomy and PLND[55]. However, in a series from MDACC 9 of 11 patients with a complete radiographic response after chemotherapy who underwent retroperitoneal lymph-node dissection with or without concomitant cystectomy, had residual disease in the resected lymph-nodes. Overall the median disease specific and recurrence free survival in these patients was lower than that for MIBC at 14 and 7 months respectively.

Multiple surgical series and retrospective studies have investigated the prognostic significance of the extent of lymph-node dissection and the prognostic outcome of these patients. These studies have found that increasing the number of lymph-nodes removed during a PLND improves disease-specific and overall survival[12, 34, 56–58]. This is true for patients with negative lymph-nodes; however, this has never been proven for patients with positive lymph-nodes. In addition, an absolute minimal number of lymph-nodes removed has not been established. A German prospective randomized study of limited versus extended PLND has completed accrual (clinicaltrials.gov NCT01215071). A SWOG intergroup randomized study of standard versus extended PLND is accruing patients (clinicaltrial.gov NCT01224665). Support of the SWOG trial will facilitate the establishment of a standard of care for the extent of PLND in patients with MIBC.

Other prognostic factors that impact the rate of recurrence and survival after cystectomy include advanced tumor stage >T3[53, 59–61] , number of lymph-nodes involved[53, 59, 61–62], tumor size greater than 3cm[59] and lymphovascular invasion [63–64]. Lymphatic and vascular invasion has been reported to be an independent predictor of survival for patients with lymph-node negative but not lymph-node positive disease. These factors can aid in identifying patients at high risk of recurrence and therefore potential candidates for cisplatin-based adjuvant chemotherapy if neoadjuvant therapy was not given.

Conclusion

The presented review reflects the discussions and debates among the panel at the SUO session based on data from the literature. Patients with MIBC should be managed with a multidisciplinary team of physicians. Limited survival benefit is associated with surgery alone in patients with MIBC suggesting a high percentage of patients have clinically undetectable metastatic disease at the time of diagnosis. Ideally surgery would be the sole modality of definitive treatment offered to patients without evidence of metastatic disease. However, MIBC is often a systemic disease and a multimodality approach with both cisplatin-based neoadjuvant chemotherapy and surgery is the best standard of care these patients can be offered. There is still a debate among the panelist and in the community regarding the ideal patients for neoadjuvant therapy T2 vs. >T2 or other high risk features. Cisplatin-based neoadjuvant chemotherapy has demonstrated a survival advantage in a meta-analysis of more than 3000 patients with MIBC, including patients with T2 only disease, although, a greater survival difference was seen within the higher stage patients in the SWOG MVAC trial. The data for cisplatin-based adjuvant chemotherapy is less compelling. Cisplatin-based therapies are generally well tolerated but a large percentage of

patients are ineligible for cisplatin. Peri-operative therapies for cisplatin-ineligible patient are still under investigation. There are no data for the administration of non-cisplatin based neoadjuvant chemotherapy such as carboplatin-combinations. In patients that have received suboptimal neoadjuvant chemotherapy a second attempt at providing high quality neoadjuvant chemotherapy should be made, if the patient is otherwise eligible and has a good performance status. If patients are unable to receive cisplatin-based therapy prior to surgery they may proceed directly to surgical extirpation with adjuvant chemotherapy considered based on pathologic findings. Chemotherapy is not definitive treatment for MIBC. Patients that achieve a complete response to chemotherapy should proceed to surgery. A large proportion of patients with MIBC that achieve a clinical ‘complete’ response to chemotherapy are understaged and risk dying of recurrent disease if they defer a radical cystectomy. The current standard for MIBC patients is cisplatin-based neoadjuvant chemotherapy followed by radical cystectomy and PLND. We trust that the summary of the panel discussions and debates will go a long way towards closing the gap between where we are and where we need to be with regards to management of MIBC.

References

1. Feifer A, Taylor JM, Shouery M, Steinberg GD, Stadler WM, Schoenberg M, Zlotta A, Lerner SP, Bajorin DF, Bochner B. Multi-institutional quality-of-care initiative for nonmetastatic, muscle-invasive, transitional cell carcinoma of the bladder: Phase I. J Clin Oncol. 2011; 29 (suppl 7; abstr 240).
2. Grossman HB, Natale RB, Tangen CM, et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. N Engl J Med. 2003; 349:859–866. [PubMed: 12944571]
3. Neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: a randomised controlled trial. International collaboration of trialists. Lancet. 1999; 354:533–540. [PubMed: 10470696]
4. Griffiths G, Hall R, Sylvester R, Raghavan D, Parmar MK. International phase III trial assessing neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: long-term results of the BA06 30894 trial. J Clin Oncol. 2011; 29:2171–2177. [PubMed: 21502557]
5. Canter D, Long C, Kutikov A, et al. Clinicopathological outcomes after radical cystectomy for clinical T2 urothelial carcinoma: further evidence to support the use of neoadjuvant chemotherapy. BJU Int. 2011; 107:58–62. [PubMed: 20560950]
6. Dickstein RJ, Grossman HB, Pretzsch SM, Karam JA, Millikan RE, Dinney CP, Kamat AM. Can we reliably identify patients for radical cystectomy without neoadjuvant chemotherapy? J Clin Oncol. 2011; 29 (suppl 7; abstr 258).
7. Pagano F, Bassi P, Galetti TP, et al. Results of contemporary radical cystectomy for invasive bladder cancer: a clinicopathological study with an emphasis on the inadequacy of the tumor, nodes and metastases classification. J Urol. 1991; 145:45–50. [PubMed: 1984097]
8. Madersbacher S, Hochreiter W, Burkhard F, et al. Radical cystectomy for bladder cancer today--a homogeneous series without neoadjuvant therapy. J Clin Oncol. 2003; 21:690–696. [PubMed: 12586807]
9. McLaughlin S, Shephard J, Wallen E, Maygarden S, Carson CC, Pruthi RS. Comparison of the clinical and pathologic staging in patients undergoing radical cystectomy for bladder cancer. Int Braz J Urol. 2007; 33:25–31. discussion-2. [PubMed: 17335595]
10. Ficarra V, Dalpiaz O, Alrabi N, Novara G, Galfano A, Artibani W. Correlation between clinical and pathological staging in a series of radical cystectomies for bladder carcinoma. BJU International. 2005; 95:786–790. [PubMed: 15794783]
11. Ghoneim MA, el-Mekresh MM, el-Baz MA, el-Attar IA, Ashamallah A. Radical cystectomy for carcinoma of the bladder: critical evaluation of the results in 1,026 cases. J Urol. 1997; 158:393–399. [PubMed: 9224310]

12. Leissner J, Hohenfellner R, Thuroff JW, Wolf HK. Lymphadenectomy in patients with transitional cell carcinoma of the urinary bladder; significance for staging and prognosis. BJU Int. 2000; 85:817–823. [PubMed: 10792159]
13. Stein JP, Lieskovsky G, Cote R, et al. Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients. J Clin Oncol. 2001; 19:666–675. [PubMed: 11157016]
14. deVere White RW, Lara PN Jr, Goldman B, et al. A sequential treatment approach to myoinvasive urothelial cancer: a phase II Southwest Oncology Group trial (S0219). J Urol. 2009; 181:2476–2480. discussion 80–1. [PubMed: 19371909]
15. Neoadjuvant chemotherapy in invasive bladder cancer: a systematic review and meta-analysis. Lancet. 2003; 361:1927–1934. [PubMed: 12801735]
16. Polychemotherapy for early breast cancer: an overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. Lancet. 1998; 352:930–942. [PubMed: 9752815]
17. Gill S, Loprinzi CL, Sargent DJ, et al. Pooled analysis of fluorouracil-based adjuvant therapy for stage II and III colon cancer: who benefits and by how much? J Clin Oncol. 2004; 22:1797–1806. [PubMed: 15067028]
18. Millikan R, Dinney C, Swanson D, et al. Integrated therapy for locally advanced bladder cancer: final report of a randomized trial of cystectomy plus adjuvant M-VAC versus cystectomy with both preoperative and postoperative M-VAC. J Clin Oncol. 2001; 19:4005–4013. [PubMed: 11600601]
19. von der Maase H, Hansen SW, Roberts JT, et al. Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. J Clin Oncol. 2000; 18:3068–3077. [PubMed: 11001674]
20. Dash A, Pettus JAt, Herr HW, et al. A role for neoadjuvant gemcitabine plus cisplatin in muscle-invasive urothelial carcinoma of the bladder: a retrospective experience. Cancer. 2008; 113:2471–2477. [PubMed: 18823036]
21. Yeshchina O, Badalato GM, Wosnitzer MS, et al. Relative Efficacy of Perioperative Gemcitabine and Cisplatin Versus Methotrexate, Vinblastine, Adriamycin, and Cisplatin in the Management of Locally Advanced Urothelial Carcinoma of the Bladder. Urology. 2011
22. Weight CJ, Garcia JA, Hansel DE, et al. Lack of pathologic down-staging with neoadjuvant chemotherapy for muscle-invasive urothelial carcinoma of the bladder: a contemporary series. Cancer. 2009; 115:792–799. [PubMed: 19127557]
23. Sternberg CN, de Mulder P, Schornagel JH, et al. Seven year update of an EORTC phase III trial of high-dose intensity M-VAC chemotherapy and G-CSF versus classic M-VAC in advanced urothelial tract tumours. Eur J Cancer. 2006; 42:50–54. [PubMed: 16330205]
24. Bamias A, Karadimou A, Lampaki S, Aravantinos G, Xanthakis I, Papandreou C, Lainakis G, Zagouri F, Soupos N, Kostouros E, Samantas E, Hatzimouratidis C, Konstantinidis C, Deliveliotis C, Pectasides DG, Fountzilas G, Dimopoulos MA. Prospective, randomized phase III study comparing two intensified regimens (methotrexate/vinblastine/doxorubicin hydrochloride/cisplatin [MVAC] versus gemcitabine/cisplatin) in patients with inoperable or recurrent urothelial cancer. J Clin Oncol. 2011; 29 (suppl; abstr 4510).
25. Sternberg CN, Pansadoro V, Calabro F, et al. Can patient selection for bladder preservation be based on response to chemotherapy? Cancer. 2003; 97:1644–1652. [PubMed: 12655521]
26. Herr HW. Outcome of patients who refuse cystectomy after receiving neoadjuvant chemotherapy for muscle-invasive bladder cancer. Eur Urol. 2008; 54:126–132. [PubMed: 18248875]
27. Dash A, Galsky MD, Vickers AJ, et al. Impact of renal impairment on eligibility for adjuvant cisplatin-based chemotherapy in patients with urothelial carcinoma of the bladder. Cancer. 2006; 107:506–513. [PubMed: 16773629]
28. Hussain SA, Stocken DD, Riley P, et al. A phase I/II study of gemcitabine and fractionated cisplatin in an outpatient setting using a 21-day schedule in patients with advanced and metastatic bladder cancer. Br J Cancer. 2004; 91:844–849. [PubMed: 15292922]
29. Bellmunt J, Ribas A, Eres N, et al. Carboplatin-based versus cisplatin-based chemotherapy in the treatment of surgically incurable advanced bladder carcinoma. Cancer. 1997; 80:1966–1972. [PubMed: 9366300]

30. Petrioli R, Frediani B, Manganelli A, et al. Comparison between a cisplatin-containing regimen and a carboplatin-containing regimen for recurrent or metastatic bladder cancer patients. A randomized phase II study. Cancer. 1996; 77:344–351. [PubMed: 8625244]
31. Dogliotti L, Carteni G, Siena S, et al. Gemcitabine plus cisplatin versus gemcitabine plus carboplatin as first-line chemotherapy in advanced transitional cell carcinoma of the urothelium: results of a randomized phase 2 trial. Eur Urol. 2007; 52:134–141. [PubMed: 17207911]
32. Splinter TA, Scher HI, Denis L, et al. The prognostic value of the pathological response to combination chemotherapy before cystectomy in patients with invasive bladder cancer. European Organization for Research on Treatment of Cancer--Genitourinary Group. J Urol. 1992; 147:606–608. [PubMed: 1538438]
33. Schultz PK, Herr HW, Zhang ZF, et al. Neoadjuvant chemotherapy for invasive bladder cancer: prognostic factors for survival of patients treated with M-VAC with 5-year follow-up. J Clin Oncol. 1994; 12:1394–1401. [PubMed: 8021730]
34. Sonpavde G, Goldman BH, Speights VO, et al. Quality of pathologic response and surgery correlate with survival for patients with completely resected bladder cancer after neoadjuvant chemotherapy. Cancer. 2009; 115:4104–4109. [PubMed: 19517476]
35. Wishnow KI, Tenney DM. Will Rogers and the results of radical cystectomy for invasive bladder cancer. Urol Clin North Am. 1991; 18:529–537. [PubMed: 1877116]
36. Dalbagni G, Genega E, Hashibe M, et al. Cystectomy for bladder cancer: a contemporary series. J Urol. 2001; 165:1111–1116. [PubMed: 11257649]
37. Kassouf W, Agarwal PK, Grossman HB, et al. Outcome of patients with bladder cancer with pN+ disease after preoperative chemotherapy and radical cystectomy. Urology. 2009; 73:147–152. [PubMed: 18848348]
38. NCT01126749 An Open-Label, Multicenter, Randomized Phase Ib/II Study of Eribulin Mesylate Administered in Combination With Gemcitabine Plus Cisplatin Versus Gemcitabine Plus Cisplatin Alone as First-Line Therapy for Locally Advanced or Metastatic Bladder. (Accessed at
39. NCT00942331 A Randomized Double-Blinded Phase III Study Comparing Gemcitabine, Cisplatin, and Bevacizumab to Gemcitabine, Cisplatin, and Placebo in Patients With Advanced Transitional Cell Carcinoma. (Accessed at
40. NCT00623064 Phase I Study of Cisplatin, Gemcitabine and Lapatinib as First Line Treatment in Advanced/Metastatic Urothelial Cancer. (Accessed at
41. NCT01342172 Gemcitabine, Cisplatin, Plus Lenalidomide as First-line Therapy for Patients With Metastatic Urothelial Carcinoma. (Accessed at
42. Donat SM, Shabsigh A, Savage C, et al. Potential impact of postoperative early complications on the timing of adjuvant chemotherapy in patients undergoing radical cystectomy: a high-volume tertiary cancer center experience. Eur Urol. 2009; 55:177–185. [PubMed: 18640770]
43. Otto TBC, Krege S, et al. Adjuvant chemotherapy in locally advanced bladder cancer (PT3/PN1-2,M0): a phase III study. Eur Urol. 2001; 39(Suppl. 5):147. (Abstr).
44. Stockle M, Meyenburg W, Wellek S, et al. Adjuvant polychemotherapy of nonorgan-confined bladder cancer after radical cystectomy revisited: long-term results of a controlled prospective study and further clinical experience. J Urol. 1995; 153:47–52. [PubMed: 7966789]
45. Studer UE, Bacchi M, Biedermann C, et al. Adjuvant cisplatin chemotherapy following cystectomy for bladder cancer: results of a prospective randomized trial. J Urol. 1994; 152:81–84. [PubMed: 8201695]
46. Freiha F, Reese J, Torti FM. A randomized trial of radical cystectomy versus radical cystectomy plus cisplatin, vinblastine and methotrexate chemotherapy for muscle invasive bladder cancer. J Urol. 1996; 155:495–499. discussion 9–500. [PubMed: 8558644]
47. Skinner DG, Daniels JR, Russell CA, et al. Adjuvant chemotherapy following cystectomy benefits patients with deeply invasive bladder cancer. Semin Urol. 1990; 8:279–284. [PubMed: 2284533]
48. Bono AV, Benvenuti C, Reali L, et al. Adjuvant chemotherapy in advanced bladder cancer. Italian Uro-Oncologic Cooperative Group. Prog Clin Biol Res. 1989; 303:533–540. [PubMed: 2675010]
49. Adjuvant chemotherapy in invasive bladder cancer: a systematic review and meta-analysis of individual patient data Advanced Bladder Cancer (ABC) Meta-analysis Collaboration. Eur Urol. 2005; 48:189–199. discussion 99–201. [PubMed: 15939530]

50. Cognetti F, Ruggeri EM, Felici A, Gallucci M, Muto G, Pollera CF, Massidda B, Rubagotti A, Giannarelli D, Boccardo F. Adjuvant chemotherapy (AC) with cisplatin + gemcitabine (CG) versus chemotherapy (CT) at relapse (CR) in patients (pts) with muscle-invasive bladder cancer (MIBC) submitted to radical cystectomy (RC). An Italian multicenter randomised phase III trial. J Clin Oncol. 2008; 26
51. Stadler WM, Lerner SP, Groshen S, et al. Phase III study of molecularly targeted adjuvant therapy in locally advanced urothelial cancer of the bladder based on p53 status. J Clin Oncol. 2011; 29:3443–3449. [PubMed: 21810677]
52. Paz-Ares LG, Solsona E, Esteban E, Saez A, Gonzalez-Larriba J, Anton M, Hevia A, de la Rosa F, Guillem V, Bellmunt J. Randomized phase III trial comparing adjuvant paclitaxel/gemcitabine/cisplatin (PGC) to observation in patients with resected invasive bladder cancer: Results of the Spanish Oncology Genitourinary Group (SOGUG) 99/01 study. J Clin Oncol. 2010; 28:18s.
53. Honma I, Masumori N, Sato E, et al. Local recurrence after radical cystectomy for invasive bladder cancer: an analysis of predictive factors. Urology. 2004; 64:744–748. [PubMed: 15491713]
54. Herr HW. Uncertainty and outcome of invasive bladder tumors. Urol Oncol. 1996; 2:92–95. [PubMed: 21224144]
55. Sweeney P, Millikan R, Donat M, et al. Is there a therapeutic role for post-chemotherapy retroperitoneal lymph node dissection in metastatic transitional cell carcinoma of the bladder? J Urol. 2003; 169:2113–2117. [PubMed: 12771730]
56. Herr HW, Bochner BH, Dalbagni G, Donat SM, Reuter VE, Bajorin DF. Impact of the number of lymph nodes retrieved on outcome in patients with muscle invasive bladder cancer. J Urol. 2002; 167:1295–1298. [PubMed: 11832716]
57. Konety BR, Joslyn SA, O'Donnell MA. Extent of pelvic lymphadenectomy and its impact on outcome in patients diagnosed with bladder cancer: analysis of data from the Surveillance, Epidemiology and End Results Program data base. J Urol. 2003; 169:946–950. [PubMed: 12576819]
58. Koppie TM, Vickers AJ, Vora K, Dalbagni G, Bochner BH. Standardization of pelvic lymphadenectomy performed at radical cystectomy: can we establish a minimum number of lymph nodes that should be removed? Cancer. 2006; 107:2368–2374. [PubMed: 17041887]
59. Ennis RD, Petrylak DP, Singh P, et al. The effect of cystectomy, and perioperative methotrexate, vinblastine, doxorubicin and cisplatin chemotherapy on the risk and pattern of relapse in patients with muscle invasive bladder cancer. J Urol. 2000; 163:1413–1418. [PubMed: 10751847]
60. Slaton JW, Swanson DA, Grossman HB, Dinney CP. A stage specific approach to tumor surveillance after radical cystectomy for transitional cell carcinoma of the bladder. J Urol. 1999; 162:710–714. [PubMed: 10458349]
61. Bassi P, Ferrante GD, Piazza N, et al. Prognostic factors of outcome after radical cystectomy for bladder cancer: a retrospective study of a homogeneous patient cohort. J Urol. 1999; 161:1494–1497. [PubMed: 10210380]
62. Hara S, Miyake H, Fujisawa M, et al. Prognostic Variables in Patients Who Have Undergone Radical Cystectomy for Transitional Cell Carcinoma of the Bladder. Japanese Journal of Clinical Oncology. 2001; 31:399–402. [PubMed: 11574634]
63. Leissner J, Koeppen C, Wolf HK. Prognostic significance of vascular and perineural invasion in urothelial bladder cancer treated with radical cystectomy. J Urol. 2003; 169:955–960. [PubMed: 12576821]
64. Lotan Y, Gupta A, Shariat SF, et al. Lymphovascular invasion is independently associated with overall survival, cause-specific survival, and local and distant recurrence in patients with negative lymph nodes at radical cystectomy. J Clin Oncol. 2005; 23:6533–6539. [PubMed: 16116151]

Table 1

Complete Pathologic Response after TURBT alone and Radical Cystectomy

Series	Year	N	P0
Pagano	1991	261	9%
Wishnow	1992	188	5%
Stein	2001	633	6%
Dalbagni	2001	284	10.7%
Grossman *	2003	154	15%

* patients randomized to TURBT and cystectomy alone

Table 2

Randomized Trials of Adjuvant Chemotherapy

Author	Year	Chemotherapy	No.Pts	Survival benefit
Skinner	1991	cisplatin, cyclophosphamide, and doxorubicin	102	Yes
Studer	1994	cisplatin	77	No
Stockle	1995	cisplatin, methotrexate, vinblastine, doxorubicin or epirubicin)	49	Yes
Freiha	1996	cisplatin, methotrexate, vinblastine	55	No
Bono	1997	cisplatin, methotrexate	93	No
Otto	2001	cisplatin, methotrexate, vinblastine, epirubicin	108	No
Cognetti	2008	cisplatin, gemcitabine	192	No
Stadler	2009	cisplatin, methotrexate, vinblastine, doxorubicin	114	No
Paz-Ares	2010	cisplatin, paclitaxel, gemcitabine	142	Yes