Optimal Timing of Chemotherapy and Surgery in Patients with Muscle-Invasive Bladder Cancer and Upper Urinary Tract Urothelial Carcinoma

William Tabayoyong, MD, PhD[a], Roger Li, MD[a], Jianjun Gao, MD, PhD[b], Ashish Kamat, MD[a,*]

KEYWORDS

• Bladder cancer • Upper tract urothelial cancer • Neoadjuvant chemotherapy • Adjuvant chemotherapy

KEY POINTS

- Survival post-radical cystectomy/nephroureterectomy is closely associated with final pathologic staging, with survival decreasing with increasing pT stage, which is attributed to associated occult micrometastases indicating the need for systemic chemotherapy.
- A multidisciplinary approach is necessary for patients with surgically resectable disease, including cisplatin-based neoadjuvant chemotherapy followed by radical cystectomy with pelvic lymph node dissection.
- The data show that neoadjuvant chemotherapy is much more beneficial than adjuvant chemotherapy for patients with bladder cancer.
- For patients who have surgically resectable disease and are noncisplatin candidates, expedient surgery is necessary; there is no role for carboplatin-based regimens in this situation.
- Advances in molecular biology, genetic subtyping, and immunotherapy are promising but cannot yet be used to supplant the role of neoadjuvant chemotherapy.

INTRODUCTION

There will be an estimated 79,030 new cases diagnosed and 16,870 deaths attributed to bladder cancer in the United States in 2017.[1] The standard of care for patients with clinically localized muscle-invasive bladder cancer (MIBC) has been radical cystectomy with bilateral pelvic lymph node dissection.[2] Survival after radical cystectomy is closely associated with final pathologic staging: patients who are pT0 have 5-year recurrence-free survival of 92%, with survival decreasing with increasing pT stage to where patients with nonorgan-confined disease have 5-year recurrence-free survival ranges between 53% and 62% for pT3b N0 and even lower (<50%) for

Disclosure: The authors have nothing to disclose.

[a] Urology, University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 1373, Houston, TX 77030, USA; [b] Genitourinary Medical Oncology, University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 1374, Houston, TX 77030, USA
* Corresponding author.
E-mail address: akamat@mdanderson.org

Urol Clin N Am 45 (2018) 155–167
https://doi.org/10.1016/j.ucl.2017.12.002

pT4 and (<35%) for pN^+ (lymph node positive) disease.[3,4] One cause for this stage-dependent reduction in survival is thought to be the presence of occult micrometastases indicating the need for systemic chemotherapy to improve survival.[2,5] Systemic chemotherapy is delivered perioperatively either as neoadjuvant therapy in the preoperative period, or as adjuvant therapy in the postoperative period. Recent expert panels have advocated for a multidisciplinary approach to the treatment of nonmetastatic MIBC that includes coordination of the timing of administration of perioperative cisplatin-based chemotherapy and radical cystectomy with pelvic lymph node dissection.[6] Unfortunately, despite these recommendations, perioperative chemotherapy is still underused in the management of surgically resectable bladder cancer.[7,8]

In this article, we review the major neoadjuvant and adjuvant chemotherapy trials for the treatment of MIBC and upper urinary tract urothelial carcinoma (UTUC) and offer recommendations based on the results of these trials and the recently updated clinical guidelines.

NEOADJUVANT CHEMOTHERAPY

Neoadjuvant chemotherapy is, by definition, the administration of chemotherapy to patients with the intent of consolidation with definitive local therapy (eg, radical cystectomy). This is in contrast with preoperative chemotherapy, which includes patients who receive chemotherapy for metastatic/unresectable disease but then ultimately become surgical candidates. Thus, strictly speaking, patients with clinical T2-T3N0M0 and T4 (prostate or vaginal wall) MIBC are candidates for neoadjuvant chemotherapy. Administration of chemotherapy in the neoadjuvant setting has several advantages.[2,5] Patients typically have better performance status and are better able to tolerate chemotherapy before surgery. Neoadjuvant chemotherapy allows for *in vivo* drug sensitivity testing (response of bladder tumor) and radiographic response is a significant prognostic indicator. Additionally, neoadjuvant chemotherapy could downstage tumors, which can make surgery easier and less morbid in some situations.

The major disadvantage of neoadjuvant chemotherapy is that one still cannot predict who will not respond to chemotherapy and the potential for delay to cystectomy in these patients could allow growth of tumor and further metastasis because it has been demonstrated that a delay in surgery of greater than 12 weeks from the time of diagnosis is associated with advanced pathologic stage and decreased survival.[9,10] This is especially true for variant histology bladder cancers with plasmacytoid, sarcomatoid, and pure squamous cell carcinoma variants being poorly responsive to chemotherapy, associated with advanced stage, distant metastases, local progression, and worse survival and disease-specific survival when compared with conventional urothelial carcinoma.[11]

Another disadvantage of neoadjuvant chemotherapy is the overtreatment of patients with organ-confined disease and no micrometastatic disease. However, this can be reduced using certain risk-adapted selection criteria (discussed later). Lastly, one theoretic disadvantage of neoadjuvant chemotherapy is the possibility of increased perioperative morbidity; however, a study of integrated neoadjuvant chemotherapy before cystectomy followed by additional administration of adjuvant chemotherapy after cystectomy demonstrated that neoadjuvant chemotherapy did not increase perioperative morbidity.[12]

Randomized Trials of Neoadjuvant Chemotherapy

Several randomized trials have attempted to determine whether neoadjuvant chemotherapy before radical cystectomy improves overall survival compared with radical cystectomy alone. With the exception of two studies mentioned later, many of these trials showed either minimal benefit or no benefit.[13–17] These trials were limited by their suboptimal chemotherapy combinations, small sample size, premature closure, and inadequate follow-up. In response to these shortcomings, a meta-analysis was performed to explain and interpret these data.[18] Combining the data of a total of 3005 patients included in 11 randomized neoadjuvant chemotherapy trials, it was determined that a 5% absolute improvement in overall survival at 5 years was associated with platinum-based combination chemotherapy. Moreover, a 9% absolute improvement in disease-free survival at 5 years was associated with platinum-based combination chemotherapy. These results represent the best available evidence in favor of the use of neoadjuvant platinum-based combination chemotherapy for patients with MIBC.

The two largest trials included in the meta-analysis that did show significant survival benefit for neoadjuvant platinum-based combination chemotherapy when their data were analyzed individually are the MRC BA06/EORTC 30894 and the SWOG 8710 trials. The MRC BA06/EORTC 30894 study was a large trial, randomizing 976 patients with locally advanced MIBC to receive either three cycles of cisplatin, methotrexate, and vinblastine