Bladder Cancer and Current Evidence for Treatment

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Occult distant micrometastasis at the time of radical cystectomy leads predominantly to distant failures in patients with locally advanced muscle-invasive transitional cell carcinoma of the bladder. Cisplatin-based combination chemotherapy enhances survival in patients with metastatic urothelial cancer. Studies evaluating adjuvant chemotherapy have been limited by inadequate statistical power. However, randomized clinical trials have demonstrated a survival benefit for neoadjuvant cisplatin-based combination chemotherapy, which should be considered a standard of care. In addition, neoadjuvant therapy may assist in the rapid development of novel systemic therapy regimens, since pathologic complete remission appears to be a powerful prognostic factor for long-term outcomes. Patients who are either unfit for or refuse radical cystectomy may benefit from neoadjuvant chemotherapy with or without radiation to enable bladder preservation.

The management of invasive bladder cancer represents a challenge for medical and urologic oncologists. The unique bladder anatomy and the biologic characteristics of bladder cancer have permitted investigators to develop postoperative adjuvant therapy as well as preoperative neoadjuvant therapy. Additionally, bladder cancer poses a significant economic burden to the US health-care system in view of the frequent surveillance procedures required and the often long natural history of superficial bladder tumors.[1] In view of these issues, the article by Sonpavde and Lerner is timely, discussing in detail the rationale and evidence for use of various types of therapy in patients with bladder cancer.

Chemotherapy for Bladder Cancer
In the 1980s it became clear that advanced urothelial cancers were sensitive to a variety of chemotherapeutic agents, and that cisplatin combinations such as MVAC (methotrexate, vinblastine, doxorubicin [Adriamycin], cisplatin) were associated with the best outcomes.[2] A series of randomized trials were then conducted to determine which single agent or regimen was superior. Sonpavde et al clearly discuss the regimens investigated, and those now considered as standards of care: MVAC, dose-dense-MVAC, and GC (gemcitabine [Gemzar]/cisplatin). The use of these approaches in patients with earlier-stage disease but at significant risk for recurrence was the next logical step.

Table 1 lists the varied options considered as adjunctive therapy in this patient population. These approaches involve multimodality care utilizing both local and systemic therapy. The rationale behind the use of neoadjuvant therapy prior to either surgery or radiation is to target micrometastatic disease that may be present at the time of diagnosis. Neoadjuvant chemotherapy is intended for patients with operable clinical stage T2-T4a muscle-invasive disease. As has been adequately described in the review, neoadjuvant therapy holds several benefits. It allows assessment of tumor response, and complete pathologic response may be used as a surrogate marker for overall survival.[3]
Chemotherapy is better tolerated prior to cystectomy or radiation therapy, and delay due to postoperative morbidity is avoided. The dose of cisplatin—one of the most active agents in bladder cancer—may be affected if the cystectomy results in urinary diversion and compromised renal function. Additionally, drug delivery may be theoretically enhanced as a result of an intact vascular bed. Downstaging with neoadjuvant therapy may allow for better surgical resection and, in some cases, bladder preservation.

Administration of neoadjuvant therapy doesn't seem to increase perioperative morbidity,[4] but there is a risk of overtreating patients. The frequency of clinical staging errors was found to be as high as 38% in a pilot study comparing clinical and pathologic staging.[5] Also, it is important to realize that chemotherapy may delay a potentially curative cystectomy for patients whose tumors were biologically destined to fail chemotherapy.

The review describes the various neoadjuvant trials. The latest is the Southwest Oncology Group (SWOG) Intergroup trial, which showed a trend toward improved survival in the MVAC-treated arm.[6] The meta-analysis reported in 2003 demonstrated a 5% reduction in death rate at 5 years, with 5-year survival improving from 45% to 50% with platinum-based therapy.[7] This analysis included patients mostly from the European Organisation for Research and Treatment of Cancer (EORTC)/Medical Research Council (MRC) trial, and hence, the results were comparable to that trial.

A similar Canadian meta-analysis of 16 eligible trials was reported in 2004.[8] Eight trials used cisplatin-based combination chemotherapy, and the absolute overall survival benefit was described to be 6.5%. A major pathologic response was associated with improved overall survival in four trials, and it was concluded that neoadjuvant cisplatin-based chemotherapy improved overall survival in muscle-invasive urothelial carcinoma, though with only a modest effect. Overall there seemed to be more benefit for higher-risk patients (cT3 vs cT2) with neoadjuvant therapy.

The authors also discuss in detail the rationale and trials utilizing postoperative adjuvant chemotherapy. Unfortunately, current adjuvant data are limited, and attempts to prospectively study this question have met with poor patient accrual. Although postoperative adjuvant therapy may be common practice for high-risk patients, this approach is not based on level 1 evidence.

Cystectomy vs Bladder Preservation
As mentioned in the review, transitional cell carcinoma is an aggressive disease, for which cystectomy is considered the gold standard of treatment. A review by Stein et al demonstrated that aggressive surgical treatment can achieve good long-term results.[9] Operating techniques have improved with the development of continent urinary diversions, leading to greater patient satisfaction.

The goal of bladder preservation is to achieve survival equivalent to that associated with radical cystectomy while maintaining the patient's quality of life. Hence, a multimodality approach including neoadjuvant chemotherapy with or without radiation therapy is undertaken. The review describes the data available in this setting, none of which are robust. No randomized trials have compared transurethral resection of the bladder tumor (TURBT) with cystectomy, nor does the addition of radiation to chemotherapy seem to provide a survival advantage.

The take-home message is that patients who undergo bladder preservation need to be a highly selected group of patients who are willing to undergo close routine follow-up with multiple cystoscopies and understand the possibility that cystectomy may be required in the course of the disease.

Biologic Markers
Finally, a discussion of biologic markers that may predict outcomes and/or tumor response and facilitate patient selection for adjuvant treatment is important. Takata et al characterized gene-expression profiles of 27 invasive bladder cancer specimens prior to administration of preoperative MVAC. They were able to identify 14 genes that were differentially expressed in responding vs nonresponding tumors. The authors proposed a numerical prediction scoring system for chemotherapy response.[10] Whether such approaches will allow clinicians to tailor therapy will depend upon further studies. In addition, p53 gene expression has been studied as a tool with which to identify poor-prognosis patients. A trial comparing MVAC to observation in cystectomy patients with mutant p53 has completed accrual.

Summary
In summary, substantial evidence supports the use of neoadjuvant chemotherapy for clinical stage T2–T4a muscle-invasive bladder cancer. The development of additional markers will improve our understanding of the disease, be useful for prognostication, and aid in selection of appropriate
treatment modalities.

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