Why consider neoadjuvant chemotherapy for muscle-invasive transitional cell carcinoma of the bladder?

Scott North, MD, FRCPC, MHPE

The purpose of the Point / Counterpoint section is to encourage vigorous and informed discussion on controversial issues in urology through the presentation of diverse opinions. We aim for a dispassionate discussion of controversies, recognizing that strong passions may exist in support of some positions.

The Canadian Cancer Society estimates that in 2007 there will be 6600 new cases of transitional cell carcinoma of the bladder (TCCB) and 1750 deaths.[1] Twenty to thirty percent of new patients will have muscle-invasive disease, and even with aggressive surgery such as radical cystectomy, it is expected that up to 50% of these patients' cancers will recur.[2] Death from TCCB in these patients is generally due to distant metastases. Therefore, the use of systemic therapy in conjunction with good local control is essential to improve cure rates for muscle-invasive disease.

Chemotherapy can be given either preoperatively (neoadjuvant) or postoperatively (adjuvant). In some malignancies, there are compelling reasons to sequence various treatment modalities in a particular order, such as neoadjuvant chemotherapy in large breast cancers to downstage the tumour and facilitate breast conserving surgery. In other malignancies, this order is reversed, with the surgery achieving local control and establishing a histological diagnosis before giving systemic treatment.

TCCB is a chemosensitive disease, with response rates ranging from 50% to 70% with the use of cisplatin-based regimens in the metastatic setting.[3–5] However, this means that many patients will not respond to chemotherapy. The use of neoadjuvant chemotherapy allows for an in vivo chemosensitivity trial. Patients can be imaged mid-way through the treatment to see if they are responding. Responders can complete their course of treatment and nonresponders can abandon chemotherapy and go immediately to surgery. If one treats in the adjuvant setting, there is no disease to follow on imaging since it has been resected, so all patients must complete a full course of therapy even though not all will benefit.

Preoperative chemotherapy may also downstage patients before surgery. In the landmark neoadjuvant trial by Grossman and colleagues[6] it was demonstrated that neoadjuvant chemotherapy using methotrexate, vinblastine, doxorubicin and cisplatin (MVAC) rendered 38% of patients pathologically free of disease at cystectomy; and the 5-year survival of this group was 85%, which is significantly better than what would be expected for all comers with muscle-invasive TCCB.

However, the major goal of neoadjuvant chemotherapy is not local control but early treatment of micrometastatic disease, which if left untreated may develop into incurable disease. Neoadjuvant chemotherapy targets micrometastatic disease while the disease burden is smallest, giving the chemotherapy the best chance to be effective. Theoretically, delaying chemotherapy until adequate postoperative healing has occurred allows the systemic disease to grow in the interim. Patients may also tolerate chemotherapy better before surgery, allowing them to receive the full course of treatment and thus all the benefits it can offer.

Finally, the most compelling reason to give neoadjuvant chemotherapy for TCCB is that, unlike chemotherapy in the adjuvant setting, there is good evidence of a survival benefit for this approach.

What is the evidence for neoadjuvant chemotherapy?

One of the most frequently quoted studies in favour of neoadjuvant chemotherapy is a phase III trial by Grossman and colleagues.[6] Patients with T2–T4a TCCB were randomized to 3 cycles of MVAC followed by cystectomy versus cystectomy alone. A total of 317 patients were randomized, and the 5-year overall survival was 43% in the cystectomy alone group, compared with 57% in the neoadjuvant chemotherapy group ($p = 0.03$, 1-sided; $p = 0.06$, 2-sided). The study was designed with 1-sided statistics, but, for publication purposes, 2-sided values had to be reported. Thus, in the final publication, this result fell to borderline significance. It should be noted that the 12-week chemotherapy program was well tolerated and there were no excess operative complications or deaths due to the neoadjuvant chemotherapy.

A larger, randomized phase III trial was conducted by the MRC/EORTC.[7] In this study, 976 patients with T2 grade 3 or T3/T4a disease were randomized to either only local treatment with cystectomy or radiation, or 3 cycles of neoadjuvant cisplatin, methotrexate and vinblastine followed by local treatment. This study demonstrated a 3 year overall survival of 50% for the local treatment alone, versus 55.5% in the neoadjuvant chemotherapy group ($p = 0.075$). While this was a negative trial, it was only powered to detect a 10% difference in survival and would be underpowered to detect a smaller absolute improvement.

As all of the neoadjuvant studies are underpowered to detect small survival differences, 2 meta-analyses have been performed using individual patient data. In 2003, the Advanced Bladder Cancer Meta-Analysis Collaboration[8] published their results based on 2688 individual patients from 10 randomized trials. They demonstrated an absolute improvement in 5-year overall survival of 5% with the use of neoadjuvant treatment. They also reported that chemotherapy should be a platinum-based combination and not single-agent chemotherapy. Winquist and colleagues[9] published another meta-analysis and demonstrated similar findings. Based on data from 2605 patients from 11 randomized trials, they demonstrated a 6.5% absolute improvement in overall survival with neoadjuvant chemotherapy. They also indicated that the current literature has not identified the optimal regimen, although most studies still used cisplatin-based regimens.

There are no definitive trials or meta-analyses that demonstrate a similar benefit for adjuvant chemotherapy. In fact, the adjuvant question is still in such doubt that an international, randomized phase III trial of surgery versus surgery plus adjuvant cisplatin-based chemotherapy is still ongoing. In Canada, this is being conducted by the National Cancer Institute of Canada and is known as NCIC BL8.

Should all patients be offered neoadjuvant chemotherapy?

Although neoadjuvant chemotherapy improves survival, definitive local management is still the most important aspect in achieving cure. Therefore, medical oncologists must ensure that if they recommend neoadjuvant chemotherapy it does not jeopardize the patient's ability to have surgery. If there is any concern that the patient will not tolerate chemotherapy or that giving chemotherapy might make the patient too frail for surgery, it should not be given and the patient should proceed directly to surgery and be re-evaluated postoperatively.

The success of neoadjuvant chemotherapy is also dependent on being able to administer the best drugs at optimal doses. The literature suggests that this is a cisplatin-based combination regimen and therefore patients need to have adequate renal function. If patients have renal insuffiency secondary to obstruction, this should be corrected before chemotherapy, if possible (i.e., ureteric stenting). If renal insuffiency is not correctable, these patients are best served by immediate surgery rather than by giving them an inferior chemotherapy regimen or significantly reducing the doses of effective drugs.

Consequently, after a thorough evaluation, if there is no medical contraindication to a cisplatin-based regimen, patients should receive a 12-week course of neoadjuvant chemotherapy. Commonly used combinations include MVAC or cisplatin plus gemcitabine. If patients are not medically fit to receive an optimal regimen, they should have surgery first and be re-evaluated afterward.

Summary

Muscle-invasive TCCB remains a major oncological problem. Death from the disease is usually

due to distant metastases. Early treatment of micrometastatic disease using neoadjuvant cisplatin-based combination chemotherapy in selected individuals has demonstrated survival advantages, compared with surgery alone. While the benefit is modest, it is consistent with the benefit of perioperative chemotherapy in other cancers. Therefore, before radical cystectomy, all patients with muscle-invasive TCCB deserve a medical oncology consultation to determine if they are candidates for neoadjuvant treatment.

Associate Professor, Department of Oncology, University of Alberta, and Medical Oncologist, Cross Cancer Institute, Edmonton, Alta.

The positions provided in the Point/Counterpoint series are presented as general information and do not necessarily reflect the personal opinions of the authors.

This article has been peer reviewed.

Competing interests: None declared.

References

1. Canadian Cancer Society. 2007 Cancer Statistics. Available: www.cancer.ca (accessed 2007 Nov 15).
2. Quek ML, Stein JP, Nichols PW, et al. Prognostic significance of lymphovascular invasion of bladder cancer treated with radical cystectomy. *J Urol* 2005;174:103-6.
3. Sternberg CN, Yagoda A, Scher HI, et al. Methotrexate, vinblastine, doxorubicin, and cisplatin for advanced transitional cell carcinoma of the urothelium — efficacy and patterns of response and relapse. *Cancer* 1989;64:2448-58.
4. Logothetis CJ, Dexeus FH, Finn L, et al. A prospective randomized trial comparing MVAC and CISCA chemotherapy for patients with metastatic urothelial tumours. *J Clin Oncol* 1990;8:1050-5.
5. von der Maase H, Hansen SW, Roberts JT, et al. Gemcitabine and cisplatin versus MVAC in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. *J Clin Oncol* 2000;18:3068-77.
6. Grossman HB, Natale RB, Tangen CM, et al. Neoadjuvant chemotherapy plus cystecotmy compared with cystectomy alone for locally advanced bladder cancer. *N Engl J Med* 2003;349:859-66.
7. Neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle invasive bladder cancer: a randomized controlled trial. International collaboration of trialists. *Lancet* 1999;354:533-40.
8. Neoadjuvant chemotherapy in invasive bladder cancer: a systematic review and meta-analysis. Advanced Bladder Cancer (ABC) Meta-analysis Collaboration. *Lancet* 2003;361:1927-34.
9. Winquist E, Kirchner TS, Segal R, et al. Neoadjuvant chemotherapy for transitional cell carcinoma of the bladder: a systematic review and meta-analysis. *J Urol* 2004;171:561-9.

Correspondence: Dr. Scott North, Cross Cancer Institute, 11560 University Ave., Edmonton AB T6G 1Z2; scottnor@cancerboard.ab.ca